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NEW EDITION 2024 NEW EDITION

14th Edition 2024

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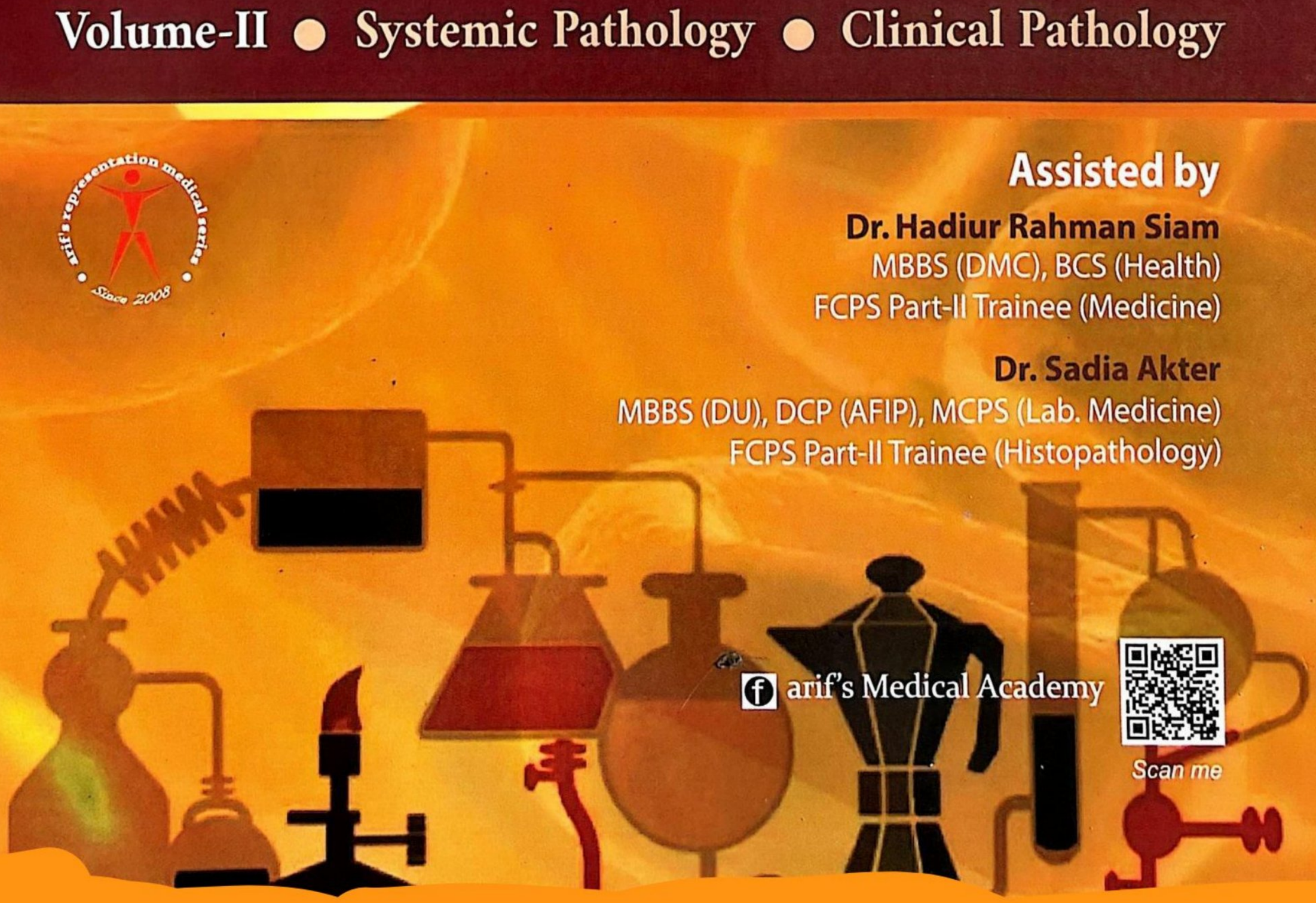

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First Edition - Published March 2010
Second Edition - Published December 2010
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Eleventh Edition - Published September 2021
Twelfth Edition - Published April 2022
Thirteenth Edition - Published February 2023
Fourteenth Edition (New) - Published February 2024

Updated up to Prof. November 2023

Fourteenth Edition-2024

Published By: Dihan Publications, Dhaka

Copy right: © 2021, reserved by the editor (CRL-23962)
ISBN: 978-984-34-0947-8

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Preface

"Bismillahir Rahmanir Rahim"

First of all, I am revealing my gratefulness to almighty Allah for his endless compassion & mercy to complete and publish the **completely new (14th) edition-2024** of this book in meantime.

This **New Edition 2024** is an exclusive one which is unique compared to the previous editions. It contains the solutions of all the Prof. questions of different Universities (DU, CMU, RMU, SUST & BUP) up to Prof. **November 2023** as well as assessment questions of different Medical Colleges of recent batches. Moreover, this edition has been divided into two separate volumes (**Vol-I & Vol-II**).

Recently **Robbins & Cotran PATHOLOGIC BASIS OF DISEASE *10th (New) edition*** has become available in Bangladesh which is **hugely different** from the ***previous (9th) edition*.** Systemic and General Pathology part has been totally **re-written** using that **new (10th) edition Robbins Pathology** and it has made the book **unique** and **totally updated**.

Use of **"BRS Pathology"-5th Edition, "Hoffbrand, Moss & Pettit"-6th Edition** and **"Dacie & Lewis"-10th Edition** along with **"de Gruchy"-6th Edition** has made the Hematology portion peerless. Moreover use of **"UNDERGRADUATE BASIC HEMATOLOGY by Dr. Mainuddin Ahmed"** has made this book special for **Rajshahi Medical College (RMC)** and other medical colleges under **Rajshahi University (RU)**. Clinical Pathology portion is totally written from **"Davidson's Medicine" – 24th & 23rd Edition** that is always preferable by the teachers. Systemic and General Pathology are totally written from **"Robbins Pathology"-10th Edition, "BRS Pathology"-5th Edition, "Harsh Mohan"-7th Edition, "Pathoma Lecture Notes"-New Edition & "Davidson's Medicine" – 24th & 23rd Edition** with the help of the lectures of different Medical colleges of Bangladesh.

In fact, no pains have been spared to make the book as attractive & appealing to the students as possible & I hope that I have been able to provide a complete guide to the students which will not only be of help in their class work, but will also give them a better understanding of the subject. The content of this book is enriched with huge amount of information that will help the post graduate entrance examinees also (MD/MS/M.Phil/Diploma/FCPS Part-I). It is also equally effective for the **BDS** students.

I have tried to make this book so complete that the readers need not to travel here and there to search this and that during examination, because everything is here that you are searching for. This will save both your time and money. **MCQ** (updated up to Prof. **November 2023**) has also been added that has made this book more effective.

I would like to thank our honorable Teachers for their proper guidance to perform best so far. I would also like to thank my dear MBBS classmates of batch SS-34, SSMC, my present & past colleagues, seniors & juniors, my friends, my students of **arif's Medical Academy** especially the students of **"Pathology course"** & also the students of different Medical Colleges in Bangladesh & all of my well-wishers. It is requested that the discrepancies, if any noticed may please be intimated to me, so that it may be taken care of in the next edition.

Frank opinions, critical comments & constructive suggestions for further improvement of the book is thankfully acknowledged.

Dhaka
20th February, 2024

Dr. Md. Arif Hossain
Sir Salimullah Medical College

Dedication

To -

My beloved Son

Arham Ibn Hossain

Acknowledgement

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SS-40: Dr.- Tareq, Bahar, Mozid, Rafi, Abir, Sajjad, Toufiq, Leon, Galib, Mahbub, Alif, Mehdi, Sobuj, Bissojit, Juel, Sujon, Riaz, Istiak, Latif, Iqbal, Anup, Rajib, Sourav , Razzak, Al Amin, Asibur, Swadhin, Bashar, Sohidullah, Nam Bashar, Subir, Rakib, Panna, Rabbi, Saddam, Hasan, Sondip, Tajim, Nayeem, Dipangon, Maruf, Nahin, Tanim, Tofael, Mahmud, Mimnu, Sriti, Busra, Sanjida, Mou, Joti, Kona, Dolon, Tanvir, Piasa, Masud, Shahriar, Jahid, Ahmad, Sifat Samrin, Sajia, Tonmoy, Abir, Eva, Shuvromonium, Sohel, Sima, Tanjila, Nasrin, Sumiya, Shahid, Kashem, Issa Ruhulla, Dhrubo, Aoyn, Simanto, Raju, Mitu, Pial, Promi, Omi, Nahian, Ejaj, Apel, Habiba, Sunny, Israt, Tamanna, Singia, Sawoda, Eti, Tanvir, Sayma, Partho, Jakaria, Rakib, Elon, Magmud, Tonmoy, Jarin, Lutfur, Sakur, Angel, Oli, Rebeka, Rakib, Ashfaq, Niaj, Baias, Farhana, Anika, Mahin, Jeba, Maysha, Jerin, Labiba, Nadia, Tonusree, Eti, Mumu, Munmun, Joydip, Shovon, Farhan, Ekram, Tanjil, Vivek, Morium, Nadia, Rifat, Apu, Pias, Hridi, Srijon, Pomi, Fahad, Pronab, Joydip, Sondip, Shams, Pritom, Rafsan.

SS-41: Dr.- Atick, Humayra, Faika, Farhan, Nayeem, Zarif, Sirazul, Babui, Mita, Mainul, Dilruba, Kallal, Sultana, Israt, Mojnu, Fariha, Abdul Hai, Arif, Shifat, Farhana, Mou, Nahid, Ruchita, Pia, Monilal, Mahfuzur, Waliullah, Sadika, Taron, Jarin, Proshikha, Marufa, Jannat, Irna, Shahla, Selim, Habiba, Brishti, Rahnuma, Foridul, Alamgir, Farah, Sanjida, Nusrat, Sujon, Sahaly, Asif, Farzana, Ashikur, Ronjit, Nusrat, Nomana, Nipa, Zarin, Raisa, Rajwana, Shuvo, Maliha, Ritu, Mansura, Airin, Tamim, Tumpa, Nondita, Lubaba, Snigdha, Porag, Selim, Shoma, Rabeya, Afzal, Jyoti, Zannat, Shithil, Sadia, Zinia, Lotif, Sadia, Saqlain, Jarjina, Tahmidul, Fatema, Nighat, Shariful, Polash, Rafsan, Shahinur, Mohiuddin, Ripa, Faisal, Tonmoy, Sumaiya, Angela, Anusua, Sadman, Tumpa, Sinthia, Diba, Fatima, Mithila, Tansu, Shorna, Taohid, Swapnil, Diki, Ashifa, Mahmud, Abdullah, Oishi, Muhaiminul, Murad, Adnan, Nazmul, Niloy, Farjana, Nowrin, Jasi, Jarin, Sarowary, Tuhina, Jisan, Tahsan, Paban Dhar, Muna, Tandra, Tariqul, Hasib, Pollab, Dip, Shibli, Rasel, Rokibul, Mokhlesur, Pavel, Samira, Shadhan, Sathi, Chondon, Sabuj, Arifur, Tasnima, Humayun, Tahsin, Nafizul, Tofique, Asish, Shapla, Razia, Pinak, Nipa, Arup, Abu Zafar, Brojesh, Mujahidul, Farhana, Moni, Sabiha, Habin, Debjani, Nabila, Adnan, Nilufa, Adeel, Mahpara, Usama, Shiran, Anjal, Ravi Sah, Safiur, Mehedi, Hafizul, Zulfiqur, Mandip.

SS-42: Noshin Anjum, Jui, Jubaida Adhara, Pranti, Rini, Binti, Tasnia, Mow, Adorsho, Toma, Ridi, Kanon, Rumi, Liyena, Tisa, Nupur, Nila, Ilma, Maha, Anu, Tesum, Susmita, Warda, Ivi, Irin, Soniya, Zinia, Supti, Susmita Das, Sathi, Munira, Eva, Laboni, Mowsumi, Sumi, Lima, Tumpa, Diti, Tithi, Wara, Tahsin, Tasnim, Tania, Riya, Nusrat, Setu, Silvi, Noshin, Urmi, Lubaba, Momo, Priyonti, Farin, Roksana, Misa, Dristy, Rima, Liza, Miftahul, Utpal, Forman, Mehedhi, Shamim, Xahid, Diptho, Mostafiz, Dhonno, Rifath, Hridoy, Toufiq, Hasib, Firoj, Tuser, Partho Protim, Niladri, Partho Sarothi, Harun, Sayem, Rasel, Fahadh, Shohel, Sishir, Shohan, Sejan, Sujon, Niloy, Tahir, Basset, Basset Arham, Sagor, Medic Mehedhi, Anik, Noman, Rayhan, Nahidh, Rasedul, Niloy, Mijan, Subrotho, Noyon, Zaki, Zisan, Shamim Reza, Nisath, Ripon, Sojib, Touhid, Siam, Munna, Asik, Sihab, Abdur Rahim, Masum, Shakil, Alhaz, Hassan, Fuhadh, Tanzim, Pritom, Dip, Soraj, Maksudh, Ali Hayder, Foisal, Habib, Mahidul, Zubair, Mosto, Utpal, Nafiu Forman, Mahfuj, Toufik, Nayan, Sujan, Rashedul, Nishat, Wiki, Dipto, Seum, Repon, Maksud, Shaima, Nahid, Ashiqul, Touhid, Shishir, Xahid, Jony, Raihan, Jannatul, Partha, Anika, Nayeem, Tesum, Fahad, Nafiu, Noman, Tahir, Imtiaz, Adan, Fahmidul.

SS-43: Abul Kalam Azad, Ruhit Acharjee, Tonmoy, Viccrom, Fahad, Abid, Afsana, Nasim Reza, Prottosh, Sifatul, Omor, Zamirul Islam, Ashik, Robin, Samiul, Nazmul, Maria, Ayesha, Mitu, Tanjina Sultana, Jabin Sultana, Jarin Anzum, Sadia Islam Shemonty, Sowmik, Rahat, Salman, Farabee, Khairul, Titu, Fahim, Nafi, Midul, Omi, Saif, Rifat, Anamul, Rohan joty, Siyam, Shamim, Sumon, Azizul Haque, Hasan, Ananya Roy, Faria Habib Disha, Prova, Tonmoy Shaha, Shoikot, Shaiful, Tahmid, Tarikul, Tariqul, Rabbi, Sadman, Asif, Samin, Tausif, Wasi, Simon, Fahim, Biplob, Rezvi, Komayel, Mobarok, Mubarack, Tanvir, Azaz, Roisul, Noman, Rashinor, Pollob, Rafsan, Humaira, Promi, Ananna, Tanzin, Sadia, Mumu, Kasif, Shrabonty, Rownak, Setu, Naznin, Bristy, Jerin, Sudipto, Papia, Avishek, Shoaib, Fattah, Yasir Arafat Nissan, Kazi Rafsan, Monirul, Sorbojit, Asif Sikandar, Sobuj, Nerob, Nisho, Samia Bipa, Anam, Ismail, Rakib, Muntasir Jisan, Labiba Tasfia, Puja, Farah Nirjhor, Nafis, Jahid Hasan, Sajib.

SS-44: Jui, Smrity, Sifat, Nazmul, Imran.

SS-45: Alica, Al Beruni, Imran, Mithun, Abir, Shawon, Jakaria, Shahriar, Mimnur, Piyal, Shakahwat, Ripon, Chondon, Joy, Sadekul, Galib, Susmit, Mahmudhul, Muneef, Zahir, Mabdullah, Nishat, Sohel Rana, Sadi, Sajib, Mithun, Tusar, Fardin, Chandan, Mahdi, Deepak, Tanvir, Asif, Soumik, Abir, Hanif, Alvi, Faysal,

Mehedi, Hasib, Ejaj, Tousif, Arif, Shinjan, Ratul, Kanon, Rokon, Osman, Tanzim, Iqbal, Beruni, Shakhirul, Emon, Risad, Musabbir, Kabirul, Saikat, Zahid, Akif, Toufik, Zisan, Rezwan, Bijoy, Sabitul, Shafeen, Riad, Shuvojit, Nahid, Ashik, Sagor, Manna, Tanvir, Tipu, Rony, Shamim, Atik, Monjurul, Alisa, Maisa, Sara, Tohura, Eshani, Anika, Ramisa, Shamosree, Zohura, Dristy, Marufa, Nibreeta, Tania, Nijhum, Nowshin, Shahnaz, Nazbet, Mimnur, Imran, Piyal , Ahnaf, Tushar, Sabit, Sammo, Piyas, Sagor, Zeshan, Atik, Saju, Riyad, Joy, Safeen, Tipu, Samim, Mehedi, Ashik, Nahid, Shuvojit, Zahir, Mahmud, Faysal, Abdullah, Tanjim, Iqbal, Munif, Azaz, Tausif, Emon, Fardin, Chandan, Mahadi, Dipok, Asib, Soumik, Shihab, Akif Yusuf, Biruni, Saharir, Rony, Sifat, Tonmoy, Mehedi, Rukon, Alvi, Osman, Abir, Hanif, Ripon, Piyal, Shawon, Sojib, Susmit, Kabirul, Saikat, Galib, Tanvir, Mussabir, Zahid, Zeshan, Kanon, Sadi, Maisha, Alica, Nini, Faiza, Sumaiya, Tasnuba, Nowshin, Nibrita, Sorna, Mitu, Nijhum, Papia, Priyanka, Nibreeta Bairagi, Tanjum Tofa, Sabrina.

SS-46: Moynul, Arshad, Niamot, Uttam, Khalid, Priyoti, Moumi, Tanisha, Nashid Kamal Nishat, Mitu Ghosh, Farjana Tasmin, Rukyea Bashira, Abdullah Al Safin, Abu Bakar, Mohaiminul Karim Fahim, Azizur Rahman, Sabbir Hossain, Ahmed Afra Anan.

BDS (SSMC)-01: Mamun, Desh, Middin, Sujoy, Sakib, Bijoy, Sydur, Shobuj, Rokon, Niaz, Hafiz, Arif, Shakhawat, Pias, Shohag, Islam, Mostafiz, Ripon, Tanvir, Raju, Amit, Momin, Majhar, Masum, Hasan, Rajiur, Saif, Habib, Prince, Al-Amin, Shovon, Hira, Mizan, Opu, Shawon, Nishat munni, Susmita roy, Afroza, Farhana dilshad, Mahmuda akthar, Ashrafunnahar rumki, Tahmina, Santa, Lubaba, Rumana, Nahid, Mahfuja, Shanta, Mahia, Faria, Tania, Sakera, Mona, Rehana, Afroza, Salma, Nishat anzum.

BDS (SSMC)-02: Arif Hossain, Khorshed, Sharif, Ariful Islam, Jahangir Mostafiz, Junayed, Johir, Tamim, Shariful, Sabbir Mollah, Saif, Habib, Sumit, Jabed, Ashraful, Ismail, Akib, Walli, Shepon, Sumon, Ashfia Leena, Leza, Papree, Jakia, Prema, Ywanna, Tania, Nishat, Bristi, Ontora.

BDS (SSMC)-03: Ananna, Fariha, Shumona, Shithe, Mustaq, Sushmita, Piyas, Kopot, Ashik, Shakila, Alom, Nisha, Rony, Nazmul, Rezaul, Miti, Jannat, Fakiha, Tanshu, Bobin, Niloy, Mahbub, Mehedi, Jihad, Shohel, Liza, Sanchita, Nahid, Shopna, Karima, Shojib, Cothica, Tabasum, Touhid, Emel, Azazul, Arif, Ismail, Shanta,Wahida, Ripa, Piya, Santa, Antora, Tropa, Jui, Himu, Muhtasima, Kumkum.

BDS (SSMC)-04: Shakil, Rayhan, Niloy Tripura, Shohag, Minaj, Iraj, Shohan, Tahmina Akter, Khadiza Era, Mehtaz, Ambia, Faman Taba, Tithy, Nahiyan, Shoiab, Sagor, Namira Mishu, Shantona Bithy, Tania, Pias, Razu, Jannat, Israt Jahan, Masudur Rahman, Shoshi, Shakhawat, Arafat, Md. Raihan, Anamul, Amrito, Arif, Sagor, Avil, Sohag, Khalid, Niloy, Iyamin, Mehedi, Sayham, Ashiq, Bayzid, Mehtaz, Munira, Tahmina, Misu, Mehzabin, Wakarunnesa, Sadia, Marzana, Sahrina, Nabila, Nusrat, Nourin, Eva.

BDS (SSMC)-06: Irin, Abir, Sumi, Julekha, Al-Amin, Limon, Tripti, Juthi, Rima, Nazneen, Khairul, Shayla, Tarif, Beauly, Shahrin, Inzamam, Tareq, Samanta, Auntora, Akash, Minhaz, Sabina Rema, Nafis, Sakib, Anni, Rasel, Tamanna, Hridita, Chahat, Mahfuja, Shahin, Shoily, Sabiha, Tanjima, Asha, Akhil, Prithibi, Mitu, Ayesha, Prema, Sadia, Simran, Habib, Sourav, Meem, Tanvir, Hamid, Saiful.

BDS (SSMC)-07: Rosni Farjana, Oishe.

Dhaka Medical College (DMC):

K-66: Dr.- Shuvro, Fazle, Galib, Faysal, Hasan, Ayon, Navid, Sadhon, Shamim Reza, Rafat, Fahad, Setu, Rajak, Saud, Sabiha.

K-67: Dr.- Mishuk, Afzal, Nahid, Ferdous, Saad, Refaya Nur, Ovik, Ikramul, Shoaib, Alamin, Rakib, Zobair, Rabbi, Sojib, Mahmud, Hasan, Foysal, Ibrahim, Samir, Saidur, Ayub, Rupa, Jebu.

K-68: Dr.- Royal, Rajib, Fayez, Biplob, Tajin, Kawser, Kamrul, Sayek, Saddam, Nabila, Parama, Sabrin, Tithi, Rajib, Hasib, Rayhan, Tasnim, Kafi, Ratul, Sourav.

K-69: Dr.- Athar, Rahul, Mostak, Ripon, Dyuti, Shamim, Imran, Sajid, Mamun, Akash, Hishan, Ishmam, Zeny, Samin, Anwar, Ashik, Hamidur, Sayem, Mukta, Shakia, Tisha, Rhidi, Tahmina, Zubayer, Mimi, Riti, Asif, Sorafat karim Miraj, Mazhar, Monoj, Arif, Romana, Bristi, Raida, Faiza, Tarifa, Tasnim Zara, Monisha Manik Piyal.

K-70: Dr.- Siam, Partho, Maria A Joyti, Abdullah-Al Mahmud, Nabila Binte Noor, Devraj Hira Akash, Nouf Abrar, Sajib, Tousif, Jannatun Nayeem preety.

K-71: Dr.- Pritom Das; **K-72:** Shaikat; **K-73:** Shihab, Sian, Asit; **K-74:** Dalton, Tawhid, Joy, Sadman, Hasib, Orko, Niamul; **K-75:** Nishat, Anirban, Raji, Shobnom, Nakib, Rimi, Konok, Keya, Shoara, Jesmin Akter, Sohel Rana Rony, Israt Jahan Jannat, Anika, Tamanna, Rifah, Anan, Afrin, Tanni, Shamima, Jakia Jannat, Tasnia, Rupa Das Polin; **K-76:** Fairuza Samiha.

Shahid Sohrawardi Medical College (ShSMC):

Sh-01: Dr.- Dip, Shisir, Bijoy, Arif, Habib, Riad, Ishtiaq, Delowar, Antara, Ifrad, Suprokash, Raton, Nazmul, Ronju, Sabbir, Mintu; **Sh-02: Dr.-** Mansur, Rasel, Milon, Tareq, Sharif, Tanvir, Razzaq, Mansurul, Asif, Safayet, Fatema; **Sh-03: Dr.-** Shouro, Shakti, Nadi, Muntasir, Bushra, Showrin Koiry, Showmya Mahabub, Redhya, Nury, Nusrat Zahan, Sabrina; **Sh-04: Dr.-** Sajid, Ekush, Saiful, Jyotirmoy, Monjurul, Mithu, Abbas, Munir, Sajnin, Arshia, Awal, Sayem, Limon, Mahir, Tanvir, Dollar, Rita, Aivi, Rasna, Mou, Shorna, Dola, Sabiha, Oishi, Megedi, Sohan, Santo, Shawon, Ovi, orik, Rahul, Prolex, Sarwat, Maliha, Moushumi; **Sh-05: Dr.-** Zalis, Monjur, Rahat, Mahboob, Shohel, Javed, Protik, Ashik, Shuvro, Liton, Jony, Amjad, Moushumi, Ghoduli, Rezwana, Shawon, Sakib, Ashraf, Omit, Rani; **Sh-06: Dr.-** Shakil Shuvo, Monsur Alam, Juty, Rafa, Abir, Sima, Royel, Faruk, Manik ,Nitu, Tonoy, Sami Asif, Shimu, Fattah, Sompod, Aniruddah, Sifat, Tisa, Bipul, Ramesh, Jahid, Sagar, Remo, Tushar, Reehan, Atik, Farah, Tanjid, Iffat Mijan, Protap, Urmi, Sabuj, Limon, Yamin, Tulip, Arafat, Sanjoy, Saad, Rasel, Subroto, Shimul, Nasif, Alomgeer, Hasan, Miazi, Refayet, Tuhin, Shakib, Mahin, Rajib, Badhon, Bappi, Rakesh, Polash, Rashed, Fahad, Sujon; **Sh-07: Dr.-** Himel, Shahed, Bappy, Saroyar, Arup, Foysal, Rohan, Morshed, Real, Sharif, Rhakhi, Sristy, Shathi, Naushin, Bornini, Shorna, Shoilash, Sagar, Yuna, Anamika, Asif, Laxman, Noman, Shailash, Sifat, Prapti, Shorna; **Sh-08:** Nahid Rezwana Priyanka, Jessy, Fariha, Saybi, Ananya, Sharmin, Sf Priyanka, Shovon Jahid, Imran, Shaikot, Tanvir, Vp Roy, Kabir, Monir, Mahfidul, Dipto, Shuvo, Rafi, Ahsan, Iqbal, Milon, Samiul, Tareq, Shohan, Mainul, Israt Tani, Saima, Tasmi, Sadia, Tania, Choyti, Himu, Zobayer, Niloy, Kudrat, Ameena, Shamem, Mehedi, Lui, Ahsanullah, Khaled, Sabuj, Fahim, Mainul, Samiul, Moshiur, Muslima, Himu, Rimpi, Ruma, Rima, Annonna, Susmita, Pima, Aliul, Firoz, Zarren Tasnim, Adytto, Shuvobrata; **Sh-09:** Feroz, Aliul, Razu, Shuvo, Asad, Sabuj, Sourav, Tanjil, Tanvir, Amit, Saiful, Rana; **Sh-10:** Alavi, Al-amin, Asif, Shahriar, Jahin, Mittad, Nihad, Tamim, Tonmoy, Nayeem; **Sh-11:** Purba, Naz, Raisa; **Sh-13:** Sumaiya Kamal, Fairooz Maisha, Sourin Banerjee, Mayeen Abir, Sadia Afrin Rimi, Indira Dhore, Nazmul Huda, Mirazul Islam Mehedi, Mohima, Shanto, Hannan, Mostafa, Maymuna Moon.

Mymensingh Medical College (MMC):

M-45: Shahidul, Sonnet, Mezbah, Fatema; **M-47:** Tasmary tanha, Nibir, Dipa, Reza, Sayem, Saikat, Rezvi, Masum, Nasir, Siddik, Tamanna, Songita, Himi, Shorna, Orchi, Tasmeri; **M-48:** Saiful, Prince, Foyez, Pappu, Mehedi, Munna, Rakib, Ashik, Lemon, Habiba, Eva, Swarpa, Mou, Tonmoy, Toffa, Nafiza, Munir, Sahdat, Sakhawat, Pallab; **M-49:** Nayeem, Ratul, Neerob, Badhon, Ahnaf, Lipu, Tusher, Royal, Masum, Monira, Farha, Popy, Bristy, Arshi, Ovi, Marium, Mahmud, Jibon, Himel, Shuvo, Shorup Malakar, Ratul, Badhon, Rasel, Ahnaf, Shopon, Sahidul, Mahadi, Akram, Pyash, Asif; **M-53:** Nayon, Samit, Nahid, Dhrubo, Anarul, Nayeem, Tofayel; **M-55:** Pobitra Nur, Abdullah Omar Razin.

Chottogram Medical College (CMC):

48th Batch - Dr.- Arup, Pranesh, Labib, Ronesh, Delower, sakib, Mishu, Sudip, Atuno, Ismail, Fahim, Ahemadullah, , Shamim, Sipul, Vashkar, Mili, Tuli, Marjia, Dalia, Subrata, Ishtiaque, Nora, Orin, Priaynka, Aminul, Dilshan, Ruba; **49th Batch - Dr.-** Russel, Ruhul, Himadri, Anup, Rishad, Noyon, Robbani, Shormi, Lina, Fushti, Shuchona, Sujon, Samuel, Najmul,Sumon, Pintu; **50th Batch - Dr.-** Sakib, Rassel, Rony, Arefin, Foisal, Mesbha, Nafis, Rifat, Limon, debashis, Jewel, Buddha, Arafat, Ashraf, Humayan, Sunny, Kaisar, Saima, Rumman, Shama, Nishi; **51st Batch - Dr.-** Russel, Nadim, Rafsan, Sumayia, moinul, Ayon, Runa, Habib, Asif, Dhiman, Mostofa, Bijoy, Tomal, Sorowar, Safique, Rajib, Shuvo, Abid, Dhrubo, Farah, Nitol, Potu Payel, Elora, Punnah, Tinu, Tanzia, Nazia; **52nd Batch - Dr.-** Shuvo, Sukanto (BDS), Bintu, Sujon, Rowshon, Mahid, Tshtiaq, Sohel, Minhaz, Saiful, Milton, Omor, Saju, Ovi, Riad; **53rd Batch - Dr.-** Raiyan, Fahim, Asif, Shuvro, Himu, Emi, Usha, Faysal, Niyaz, Mamun; **54th Batch** - Ratin, Shimanto, Sumaiya, Tanju, Ameena, Prince; **56th Batch** - Murad, Mamun; **57th Batch-** Tothi, Adnan, Hasnat, Shahriar, Ayon; **58th Batch-** Nirbas Wadud Khan; **60th Batch-** Redeta, Rifah Sanjeedah, Mushfika Sultana.

Cumilla Medical College (CoMC):

CoM-15 : Dr.- Rahat, Zia, Atiq, Minhaz, Ashraful, Anisur, Mahbub, Mobarak, Monjurul, Arifullah, Sayed Ariful, Merajul, Sharif, Mohabbat, Shawon, Shuvo, Jamal, Yasir, Maruf, Mehedi, Amit, Imad (Pak) and Sadeq.

CoM-21 : Naina, Anika, Badhon; **CoM-22 :** SM Raahim, Rony, Rakib, Reza, Salman, Zawad, Niloy, Akib, Arefin , khaled , Ovishekh, Najmul, Ruma, Sadia, Neepu,Trina, Dipa, Supriya, Mim, Zoynob, Shanta, Oshin, Ayeda, Lima, Turna,Trisha.

CoM-23 : Sabbir, Ashik, Promit, Adeeb, Arif, zubayer, suprio, Bithin, Harun, Fahad, Asif, Shoyeb, Gias, Towfik, Ani, zinat, progga, Mukta, Mumtahin, Anika, Rimi, Naomi, Shaikat, Tanvir; **CoM-27 :** Jannatul Hoque, Rumaiya, Sarafat Upol, Bashir Ahammad.

Rajshahi Medical College (RMC): Dr.- Toufiq, Soyeb, Sabina, Riyadh, Harun, Rafat, Nadira, Sowmitra, Rimi, Niloy, Sabina, Sumon, Mamun, Suchi, Bakar, Anup, Anika Hasan; **53rd Batch-** ***Dr.-*** Mukti, Robiul, Aminur, Samiul, Emon, Barik, Mamun, Hakim; **54th Batch-** Soikat, Samrat; **55th Batch-** Zohurul Islam Polash, Shimul, Al amin, Sanij, Bina, Rocky, Aditi Hasan, Abdur Rahman, Mahbub, Imran, Ashmita, Ayesha, Mim, Rimu, Mamun, Nice, Maria, Ashik, Tonni, Nowrin, Sumon, Sudipto, Dipto, Shahidul, Shanta, Munni, Munira, Tasnim; **56th Batch-** Imran, Sakhawat, Rasna, Arif, Azad, Shariful, Mehedi, Kamrul, Sayeed, Jafor, Akash, Rokon, Samrat, Galib, Supriyo, Shaik; **57th Batch-** Mohim, Bashar, Farhana, Tushar, Forhad, Masum, Jubayer, Shakil; **58th Batch-** Afia, Wasima, Puspo, Tawhidul, Shreya, Abida Binte Anwar, Sushmita Khan, Sara, Madhurja; **59th Batch-** Nahiduzzaman Usno, Nazia Rahman, Masum, Abu Hossen, Gourob Saha, Najmus Shahadat, Farhana Afrin, Sanjida Yesmin; **60th Batch-** Nusrat Jahan, Mizanur Rahman, Law a Salman.

Sher-E-Bangla Medical College, Barisal (SBMC):

SB-40: Dr.- Shabukta-gin, Juel, Nurul Huda, Masum Billah, Prince, Shahid, Rabbi, Mohsin, Shamim, Onik, Ruhul amin, Munna, Opurbo, Sudipto, Bristi, Esha, Salger, Sadi, Asif, Mitul, Morshed, Azim, Anam, Riad, Lion, Sojib, Said, Rifat, Lipu, Pantho; **SB-42: Dr.-** Nadim, Shuvo, Ashik, Koushik, Sumon, Ajit, Rimi, Sumaiya, Tuli, Jolly; **SB-43:** Aumi, Arif, Sandhan, Faysal, Mamun, Rafi, Anwar, Ayon, Rumi, Rafidul, Mumu, Moon, Kanta, Mim, Mohona, Najia, Mimma, Bushra; **SB-48:** Israt Jahan; **SB-49:** Nasfin Jahan Nisha, Israfil Husain, Maruan Hossain, Asadullah Al Galib, Arghya Biswas.

Sylhet MAG Osmani Medical College (SOMC):

48th Batch: Mobarak, Chanchal, Pobon, Mamun, Tamim, Mishu, Mizan, Aminul, Minhajul, Estashamul, Nahid, Amit, Anisul, Raju, Asif, Saiful, Sharif, Tahmina, Nafisa, Tajnin, Nusrat.

49th Batch: Raiyan, Imam, Zahid, Shahadat, Rafik, Shafik, Rabiul, Badshah, Jack Manna, Atik, Sakawat, Zeesan, Ashik, Mintu, Benijir, Ayesha, Setu, Tithi.

50th Batch: Jamil, Mazed, MAK, Rizbih, Habib, Arefin, Turab, Arif, Murtaza, Sowrov, Ashfak, Saifullah, Shakil, Harun, Sumon, Sanzid, Zesun, Kawser, Nayeem, Rakib, Mamun, Anupom, Trina, Metu, Farida, Shanta, Jhinuk.

51st Batch: Jahik, Hasib, Siam, Sakib, Abid, Masud, Jamir, Rezaul, Emon, Kamrul, Noman, Sajib, Rayhan, Sajid, Xabed, Rakib, Tamim, Sabbir, Imran, Shanto, Habibur, Hasan, Imran, Esha, Saddam, Asrat, Arifa, Jui, Sumon, Turjo.

52nd Batch: Azgar, Shahriar, Alkas, Bappi, Shaker, Rauf, Nur Tamiz, Mostafiz, Mahfuz, Monsur, Osman Khan, Osman Goni, Sabbir, Munif.

53rd Batch: Jawad, Pranto, Sohrav, Sejul, Azim, Mahfuz, Alauddin, Sazid, Miraz, Saddam, Abdul Momin, Taiful, Junayed, Bakibillah, Hridoy, Arif, Juel Rana, Mehedi, Zubayer, Mazhar, Mehrab, Abdul Kalam, Monir Khan, Masudur Rahman, Wazed Razu.

54th Batch: Jahid, Tuhin, Noor Kashem, Lione, Siam, Abu Bakar, Asif, Nijhum, Riad, Tareq, Ashraful, Mahi, Porag, Sohag, Shium, Helim, Nazmul, Abdul Bari, Thoughtless Shohag, Suruj, Rahat, Anik, Arif, Golam Kibria, Rakibul Rabbi, Tawhid, Shabab, Ripon Mia, Hasan, Turzo;

55th Batch: Afia Fahmida Nizhum.

56th Batch: Labbatul Jannat, Sadia Hoque, Mothmayena Meave, Samiha Sultana, Fatema Jemy, Kamolika Chakrabarty Disha, Farhana Islam, Zannatul Ferdous Disha, Jannatul Ferdous Tonny, Tripty, Naoshin, Tahia Jannat, Moutushi Islam, Rhyan Jannat, Jerin, Umme Salma, Fahima, Tania Akter.

SOMC 1st BDS: Sakib, Bappi, Mahmud, Saddam, Nisa, Juthi, Naznin.

SOMC 2nd BDS: Harun, Johny, Shamim pasha, Shahed, Mahmud, Mohin, Tofazzal, Dipa, Parsia.

SOMC 3rd BDS: Ikram, Sulaiman, Sayem, Tofayel, Nasim, Rahma, Tomalika, Khadiza, Salma, Tonni.

SOMC 4th BDS: Lalon, Sakhawat, Jaman, Noman, Riad, Tafhim, Talha, Saddam.

SOMC 5th BDS: Takbir, Hasanul, Tamjid, Nazmul.

Khulna Medical College (KMC):
K-15: Dr.- Upananda, Asif, Epu, Chayan, Foysal, Kowshik, Bappa, Mehedi; **K-16: Dr.-** Prokash, Ayon, Anis, Firoz, Liton, Anik; **K-17: Dr.-** Himadri, Ucchash, Joni, Bappa, Miraj, asif; **K-18: Dr.-** Adnan, Bithi; **K-22:** Sadia afrin, Lalon Sarker, Arnab Boksi; **K-25:** M.M. Foysal; **K-26:** Taj, Tuli, Radia, Arpita, Jannatul Mawa, Humira Mahjabin, Sefat; **K-27:** Rehnuma Masud, Biplob Saha, Masrur Ahsan Zidan, Anu Radha Das, Sucheta Ranjan Mistri, Nishat Anjum, Samprity Paul, Tasnim Alam, Nawrin Tasnim, Natasha Islam, Sadia Afrin Rimu, Nargis Akter, Raunak Nazifa Mashfi, Halima Tus Sadia, Sadia Sultana, Sadia Islam.

Bangabandhu Sheikh Mujib Medical College (BSMMC), Faridpur: Dr.- Shohag, Sani, Reza, Shahidul, Saif; **F-26:** Tasfia Haque Arthi, Sharmin Sathi, Maliha Zahir, Supti Roy; **F-27:** Salma Akter, Anamika, Rummana, Fairuj Anika, Kawsar, Akash, Anika Tasfia, Hafsa Akter, Sazzad Shezan.

Rangpur Medical College (RpMC): Batch-37: Dr.- Kayes, Dhali, Asad; **Batch-38: Dr.-** Avijit, Himel, Mursalin, Prianka, Fine, Toufique; **Batch-47:** Shamim Sarker, Armin.

M Abdur Rahim Medical College, Dinajpur: Batch 17th – Dr.- Adnan, Krishno, Shib, Sayem, Tairan, Atia, Mohona, Mazed, Rakibul, Shahjadi, Mamun, Sanjana, Amio; **Batch 27th** – Sabrina Shuchi, Shahriar Hossain, Abdulla Al Hameem.

Shahid Ziaur Rahman Medical College (SZMC), Bogra: Mamun, Mokhles, Jewel, Ruma, Jinnat **(15th)**, Najat, Sharmin, Sumi, Amir, Asim, Alo, Hadi **(16th)**, Atiq, Arif, Luna, Mouli **(17th)**; Rifat **(26th)**; Nishat Jahan Ria, Farhana Tasnim Mim, Moontaha Binty Shams, Arnob, Afia Sultana, Nadira Jahan Lia **(27th)**; Mayesha Afroz **(28th)**.

Pabna Medical College (PMC):
1st Batch- Zim, Ruhul, Xehan, Rupom, Imtiaz, Pluto, Bipu, Sithi; **2nd Batch-** Lemon, Rahat, Yousuf, Nazmul, Shimul, Rashed, Sourov, Rahul, Babul, Timir, Imran, Susen, Rani, Shawon, Lipi, Neha, Mouri; **3rd batch-** Touhid, Rehan, Shovon, Chondon, Sujan, Jakir, Sayma, Tamanna, Sumaiya, Mahbuba, Panna, Shibani, Afsana & Shorna; **10th batch-** Syeda Usaila Rahbar, Nirbana, Zuayria, Rina Akter, Fariha Tasneem, Golam Sarwer Konik, Ashika Ahmed.

Cox's Bazar Medical College:
1st Batch- Dr.- Tahmina Nipu, Sabrina Reshma, Tasnova Islam, Abu Tayab, Riku, Abid; **2nd Batch- Dr.-** Muhammad Niloy, Ripon Chay, Jannatul Ferdaus, Rubina Akter, Arnab Chakma, Saurav Dutta, Arif, Shafi, Nishat, Maun, Jani, Jackson; **3rd batch- Dr.-** Kazi Nokib, Sharmin Jitu, Falguni das, Rajin, Ashik; **4th batch-** Md. Raihan, Rahin ul Kabir, Galib, Partho, Sayema, Mojaen, Pulok; **5th batch-** Rifat Islam, Md. Tajul, Noman, Ananta Borman, Sotan Prem, Tahmid, Rajib, Rakib, Milon; **6th batch-** Ratnam Arjun, Emon, Abid, Hossain, Shahin, Nabil, Pias, Tanza, Munia, Puja, Tamanna, Sananda, Pashla, Irom, Punom, Brishty, Juthi; **10th batch-** Purna Paul.

Abdul Malek Ukil Medical College, Noakhali: Batch-09: Tanjina Akter, Nur Hossain; **Batch-10:** Mehedi Ahmed, Sabbir Hossain, Nur Mohammad Naeem, Farhana, Sanwar, Mumtahina Mim, Showgat Chowdhury Ovi.

Colonel Malek Medical College, Manikganj: CMMC-04: Fatema Tuz Zohora, Anika Tasnim, Faysal.

Satkhira Medical College (SMC):
SMC 01: AB Arman, Apu Mazumder, Sabbo Sachi, Nazmul Hasan, Udaya, Manna, Momin, Muktadir, Khan, Safiullah, Minak, Mamun, Prodipan, Mithun, Pias, Raprue, Titu, Alamgir, Tanvir, Rokib, Hasan, Shaon, Nazmul, Riyadh, Lucky, Tamanna, Sara, Nushra, Tania, Promi, Aurin.

SMC 02: Sharif, Roni, Zaman, Mamun, Ahsan Habib, Anamul, Aslam, Selim Reza, Nira, Broti, Sabrin, Toma.

SMC 03: Sumon, Moin, Rahat, Shamim, Khalid, Rajib, Ashik, Elham, Shuvo, Humayun, Setu, Ashraful, Aminul, Akanda, Newton, Kabir, Shabuz, Shibbir, Imran, Ibrahim, Partha, Riaz, Robi, Asit, Shahed, Emdad, Ratul, Brishty, Sabina, Akhi, Jeba, Lima, Asma, Mahmuda, Vabna, Keya, Fariha, Nishi, Mitu, Nishita.

SMC 04: Abdullah, Anik, Nayem, Shakil, Habib, Noman, Bashar, Raju, Sudipta, Ashfaq, Sajjad, Gafur, Nayemur, Mong, Arif, Belayet, Mobarak, Hasib, Robiul, Altaf, Arusha, Tania, Irin, Tanjena, Pinky, Asma, Etu, Lima, Monira, Sharmin; **SMC 06:** Fatima Tasnia.

Jashore Medical College (JMC):

1st Batch: Jahid, Fahad, Towhid, Anonna, Oly, Abid, Bivour Chakma.

2nd Batch: Konok, Delwar, Jessy, Rubana, Maria; **3rd Batch:** Alam, Feroz, Topu, Lucky, Tabassum, Kader, Silvia, Nayeem, Nasir, Nasif, Sapon, Partho, Mamun, Bonny, Akhi; **4th Batch:** Arpon Roy, Md. Jowel Mia, Tanmoy Saha, Shubroto Debnath, Ashrafunnahar Ananya; **8th Batch:** Shumaiya Shammi Bili, Sara Meherin, Shayma Azmi Nishu, Humayra Binte Zohir, Maher Afrose.

Sheikh Sayera Khatun Medical College (SSKMC), Gopalgong:

1st Batch - Maruf, Ashik, Prince, Limon, Zihad, Onj, Robin, Muktar, Nibir, Muzahid, Anup, Dipan, Jahangir, Puspita, Shoshee, Radia, Ajijar Rahman Rony, Jakaria Parvez, Shahabi, Muktar, Noman, Rubel, Afsar, Raju, Mostofa; **2nd batch** - Mehedi, Shuvo, Anis, Noman, Hasan, Puspen, Mohobbot, Junayed, Tonmoy, Tuhin, Dip, Fuad, Kyaching Marma, Amit, Pias, Shoshi, Panna, Ashima, Nitu, Eshita, Jesmin, Irani, Suma; **3rd Batch** - Shuvasis, Niloy, Ibrahim, Tasin, Romjan, Hafiz.

Shahid Syed Nazrul Islam Medical College, Kishoreganj:

SN-1: Nirob, Munna, Imran, Pritom, Mahir, Jahid, Mamun Ur Rashid, Ashraf, Iqbal, Nazia, Majeda, Yamun, Sania, Akhi, Tipa, Suraiya, Mimu, Bristy, Sabbir, Sonia, Piu, Manzuma, Hashi. Moni.

SN-2: Munni, Silvy, Papia, Shathi, Moutushi, Moon, Mukta, Tanjin, Rubya, Tasmia, Shakil, Nipu, Ahmad, Tanil, Roman, Sweet, Shovon, Lizon.

SN-3: Shajon, Alo, Shamim, Riman, Shahin, Rumon, Ashraf, Aminul, Upoma, Rehnuma, Shashi, Lutfar, Anika, Bithi, Shoyeb, Tamjid, Nayan, Srijona, Atika, Ema, Israt, Jamil, Anni, Nova, Antora, Trisha; **SN-7:** Tabirul Islam.

Shaheed M. Monsur Ali Medical College, Sirajganj:

Batch-01: Shaheb, Recon, Roman, Tamim, Monsur, Sifat, Kripanto, Plabon, Dipto, Shantu, Nandi, Mahabub, Abdullah, Rana, Sohagh, Tonmoy, Imran, Rana, Antora, Nisha, Mohona, Nasrin, Suchona, Nawshin, Tamanna, Sanjida, Sithi, Norin, Kanij, Erina, Sifat, Swarna, Upoma, Moumita, Tisha, Shama, Aleya, Pingky, Afiya, Keya, Nikhat, Eshita, Mishu, Sushmita; **Batch-02:** Nahid, Reza, Muktadir, Sifat, Sohan, Akash, Sahwon, Sojol, Rizu, Rahat, Aslam, Mahmudul, Anup, Shadi, Toufique, Monir, Ripon, Humayon, Sunny, Mahfuzur, Rakib, Hema, Diltaz, Simmun, Shams, Shimu, Pakhi, Rafsana, Sharmin, Shanta, Jebin, Dip, Rafia, Habiba, Nazia, Neha, Shanta, Shahnaz, Sabrina, Hridi, Maliha, Ambiya, Nafisa, Rakib, Aslam, Zuel, Rafzana, Shimu, Shams, Shuhi, Sojol, Akash, Rakib, Bappi, Soma, Tasnim, Toufiq, Sumaiya, Jebin, Shawon, Shorna, Mahfuz, Nilanjona, Hema, Shohan, Sunny; **Batch-04:** Raini Jannat, Sumaya.

Kushtia Medical College:

1st Batch- Sanower, Abu Shahed, Talha, Abdul Karim, Rajon, Badhon, Debasish, Shihab, Shaon, Babor, Amal, Sakib, Uzzal, Jahid, Arifin, Muhaiminul, Najmus Sakib, Tonny, Irin, Momo, Suravi, Aysha, Monami, Rakiba, Nodi, Hanufa, Chamely, Nipun, Suvra, Jebin, Prianka, Nila, Srabonti, Asma, Nahid, Simu, Masuma, Disa, Kakoli, Prima, Sathi, Fatema,

2nd Batch: Shamim, Farhan, Saidur, Rafin, Mishkat, Sazzad, Al Aksa, Suvro, Faysal, Tajul, Manik, Tanim, Krishna, Tamim, Habib, Tomas, Abir, Istiaque, Amin, Minhaj, Sadik, Ibrahim, Raihan, Samrat, Meem, Karz, Mawa, Sadia, Maliha, Poly, Mukti, Nova, Tabassum, Tuli, Sumaiya, Nipa, Tanu, Runa, Aunamika, Tajkia, Esha, Sakila, Supta, Sharmin, Tanha, Laila, Keya, Saima, Shara.

3rd Batch: Saimum, Asif, Sarif, Sumon, Amim, Nishat, Aminul, Dip, Bappa, Sarjil, Shaon, Hasan, Zami, Raihan, Ilias, Masum, Tamanna, Urmi, Afrina, Songita, Dola, Priyanka, Akhi, Shaila, Prema, Monisha, Borna, Ontu, Jerin, Hridi.

4th Batch: Hasib, Sakib, Prosanto, Jinnah, Imran, Rony, Punorn, Nayem, Belal, Royel, Reza, Ehsan, Sanjida, Srea, Sweety, Nirma, Tonuja, Moly, Samanta, Mou, Jhora, Sushmita.

5th Batch: Sajib, Ono, Atik, Shaon, Jafor, Supto, Shuvo, Najmul, Suchi, Ontora, Any, Lora, Sornali, Adiba, Shaila, Mridula, Nafiza; **6th Batch:** Ahammod Joardar, Ripon Miah; **7th Batch:** Aparajita Nandy, Khadiza, Tamanna.

Patuakhali Medical College:

Batch-1: Abdullah Zubair, Nazmus Sakib, Jahirul Islam, Tanvir Anik, Rashedul Islam, Mohsin Alam, Akbar Hossain, Muntasir Billah, Abu Bakkar Siddique, Shahriar Sagor, Faizur Rahman, Mahfuzur Rahman; **Batch-4:** Sofola, Rasel.

Sheikh Hasina Medical College, Jamalpur: Batch-3: Tanvir Ahamed Sabbir; **Batch-5:** Nayeem Hossain.

Sheikh Hasina Medical College, Habiganj: Batch-1: Nishita Dash Hridi, Mostafijur Rahman.

Chandpur Medical College, Chandpur: 1st Batch: Sadman Sakib.

Rangamati Medical College:

Batch-1: Nadim Mostofa, Rafiqul Islam, Rayhan Uddin, Snehashis, Mujibul, Sourav, Suhan, Fuad, Sagor, Sakib, Rubel, Jahid, Zakir, Mishu, Prahar, Rafi, Blessing, Pabon, Nurul, Priom, Tasnim, Sweety, Mithila, Mahera, Tanee, Ilteza, Arzu, Tropa, Epru, Ayesha, Sadia, Liza, Sumi, Muna, Maliha, Ruhi, Laboni, Afiya, Sumaiya, Jannatun, Suil, Asmita, Maraching; **Batch-2:** Sakibul, Anisur, Rayhan, Tareq, Ifrad, Monir, Mushfiq, Saiful, Dipu, Sojib, Sabith, Foyez, Shuvo, Ratul, Shakwat, Joy, Arnob, Shrikanto, Dipto, Alin, Rijvi, Abraham, Chayan, Sayed, Nayeem, Maniya, Tania, Anima, Habiba, Tanzina, Samia, Shranoni, Nurani, Turna, Mysha, Shimla, Moon, Manowara, Seema, Saiful; **Batch-3:** Sayed Hasan.

Mugda Medical College, Dhaka:

MuMC-01: Ankon, Sazib, Nayeem, Mehedi, Ayon, Fahim, Zihan, Shariful Alam, Bidushi, Mehzabeen, Priyanka, Anannya, Ritu, Hafijul, Irfan, Borshon, Anoy, Nabil, Shoity Moni, Kushol, Mahin, Mahmudul, Nabil, Awal, Rifat, Shuvo, Rafayel, Nusaer, Hafiz, Maktum, Zubaer, Barid, Arnob, Noyon, Disha, Tamanna, Prima, Priyanka, Mukta, Anabil, Afsana, Sabrina, Puspo, Shukh, Maria, Mahim, Turabi, Shayla, Rakiba, Bidushi, Anannya, Nusaer, Hafiz, Maktum; **MuMC-02:** Purubi Sarker; **MuMC-03:** Mallik Nadim Farhan Oni, Aurpa, Bristy Roy.

President Abdul Hamid Medical College: AH-03: Foysal Ahmed Souvik; **AH-05:** Aditi Das.

Shaheed Taj Uddin Ahmad Medical College, Gazipur: TA 02: Nahid; **TA 03:** Salehin, Rabeya Tasneem Kakon; **TA 04:** Tanvir, Sagar, Kamal.

Dhaka National Medical College (DNMC): N-15: Saha Showrav Anjan; **N-19:** Sohan, Aiman, Pinki, Imran, Barkat, Mim, Bushra, Lamiya, Shahriyar, Daood, Lija, Shaon, Naif, Arif, Shoikat, Ovik, Abir, Rifat, Tomal, Mubin, Banna, Mahmud; **N-20:** Ishtiak Emon, Ashiq Anwer, Rakib Hasan, Rumpa, Suman, Shurid, Afsana, Nahid, Logna, Pial, Amio, Shohan, Arup, Nidul, Pulok, Nipu, Taohid, Nawaz.

Jahurul Islam Medical College (JIMC): J-15: Dr. Priobroto; **J-16: Dr.-** Asif, Soma, Khalid, Rini, **J-17: Dr.-** Orcho, Pias, Amy, Raju, Navina Anik, Annaya, Bushra, Probal, Borsha, Sharmin, Ratan, Ripa, Munim, Redwan, Ridita, Sajid, Nupur, Jui, Zen, Adrita, Tasfi, Orag, Sumon, Mukta, Nipa; **J-17:** Sajib, Partho, Onik, Rana, Hasan, Rabbi, Rahat, Sakib, Sathila, Tonni, Sathi, Mabruka, Tasnim, Mukta, Iffat, **J-19:** Milon, Antu, Pritom, Shafayet, Jewel, Khusi, Nahiyan, Zeko, Atiq, Samia, Akhi, Nafisa, Pinki, Munira, Irena, Monica; **J-20:** Afifa, Rezwan, Newyaz Sharif Ahmed (Nosu), Anu, Imran, ; **J-21:** Tanji, Emon, Sashi, Lutfa, Tanvir, Aumee, Tonni, Doli, Shikto, Mun, Rafsan, Joy, Jamim, Vikar, Labib; **J-22:** Atul, Shuvo, Tahsan, Akash, Siddik, Touhid, Priyanka, Minnat, Shuvon, Mustafiz, Indrila, Rupa, Lima, Pojja shah; **J-24:** Noman, Himel, Sagor, Mehedi, Arpa, Jui, Setu, Liga; **J-25:** Jerin, Areefin Nirob, Dhruba, Ratri, Zakia, Ifty, Noman, Arman, Purna, Arafat, Adeeba, Pavel, Dip, Shuvo, Tahmid; **J-26:** Monsur Alam; **J-27:** S.R. Faud Hasan, Fariha Sarker, Abdullah Al Masud Hasib, Hasbi Ahsan Sreejan.

Enam Medical College (EMC): EM-3: Razzak, Lincon, Salauddin, Ahmed, Mahmudul Hasan, Israt Binte Rafique, Nujhat Ferdous, Farhat; **EM-5:** Ivan, Antu, Samira, Sahariar; **EM-14:** Mia Muhammad Abdullah; **EM-15:** Chinmoy.

Holy Family Red Crescent Medical College: Batch-18: Anika Ontu; **Batch-19:** Israt Jahan Joti, Tajkeya Tun Nur, Forhaduzzaman, Anindita Roy, Tasmia Kaium, Nobomita Mim, Sumaiya Binte Azad, Shajeeb Sarkar.

Bangladesh Medical College (BMC): BM-22: Taneem, Somir, Abdullah, Tanvir, Tasdiq; **BM-25:** Nahid Hasan Rifat, Nadia Binta Ali, Adnan, Tasin, Samantha, Pia, Dorothy; **BM-26:** Iqbal, Sadat, Junaid, Oishy, Fuad, Saikat, Hasmat, Arif, Kayes, Mridul, Imran, Hasmat; **BM-27:** Shourov, Sadman, Rafsan, Rifat, Rafi, Fahim, Fardin, Anik, Sajal, Arefin, Arony, Mumu, Nishi, Anoma, Mim, Polin, Raju, Shakila, Nahid.

Khawaja Younus Ali Medical College (KYAMC): KYA-03: Saikat, Yusuf; **KYA-05:** Shahin, Zahid, Faisal, Monir, Mahmud, Sandhi, Himadri, Enamul, Sajal Debnath; **KYA-12:** Sharjana Zafrin.

International Medical College (IMC): Batch-9: Firoz, Aziz, Dulal, Shovon, Foysal, Sufian; **Batch-8:** Maruf, Mehdi, Niaz, Tomal, Shuvo; **Batch-7:** Tanzida, Fatema, Nusrat, Sadia, Eti, Ashfaque.

Tairunnessa Memorial Medical College (TMMC): TM-2: Nadia, Rasel, Prasun, Shawon, Shikha, Sheyam; **TM-6:** Onika, Gofran, Suborna, Orin; **TM-10:** Milton, Rubel, Rony, Rifat, Maynul, Biplob, Ovijit, Fattah, Ibra, Azmiri, Munni, Hemely, Jesmin, Mitu, Mehraj, Ishfaq, Hameem, Resham, Tabassum; **TM-11:** Mehedi, Ashik, Tanvir, Shawon, Hridoy, Javed, Tanvir, Shova, Nahid, Sajol, Tania, Hafsa, Arifa, Saoda.

Ibn Sina Medical College, Dhaka:
ISMC 05: Md Ibrahim, Amran Hossain Chowdhury, Nasrin Sutana, Saila Siddiqua; **ISMC 06:** Ruhul Amin, Nadia Fatima, Tasfia Tarin Suchi, Prince Shariar, Md Nabil; **ISMC 07:** Jwel, Nafisa Tabassum, Kawser Ahamed, Humaira; **ISMC 08:** Abbas, Shimul Ahamed, Tabassum, Fahmida Akter Zahan, Rony; **ISMC 09:** Md. Shakil Ahmed, Alimuzzam, Rifat Mahin, Prince, Rifa Tasfia, Sadia Tasnim, Redwanullah, Atikuzzaman, Shadman, Zubayer, Abir; **ISMC 10:** Rounok Hasan Rimi, Mostafiz, Anika, ATM Sumon, Saiful, Rijvy, Ahmed Rony, Mostafiz; **ISMC 14:** Maliha Rahman.

Green Life Medical College, Dhaka:
GMC-1: Dr.- Maisha, Nashin, Saikat, Anabeel, Sakir, Touhid, Zobaer, Meshuk, Arko, Shezan, Banna, Umor, Mou, Saiful, Jishan, Rizvi, Anika, Rana, Oni, Raihan, Vaskar, Shetu, Akif, Labonno, Koushik, Uttam; **GMC-2: Dr.-** Shuvo, Asif, Monowar, Tawfique, Farhanaz, Tafsir, Nafis, Reba, Touhid, Mukit; **GMC-3: Dr.-** Sabbir, Bondhon, Nabil, Arnob, Anik, Rumpa, Zumana, Martin, Pijush, Sarjil, Santu, Anik, Dev, Papri, Ayesha, Rafia, Raziv, Saniya, Jinnat, Sumon, Monir, Shuvo, Salma, Partho, Shilpy, Tasmin, Rasel, Tanmay, Nazim, Anwar, Bapon, Afsana, Sananda, Shafeen, Reza, Tamjid, Tanji, Mahim, Farabi, Anik, Das, Nazila, Antor, Sazzad, Sajib, Rony, Sheba, Richi, Ripon, Moumita, Zafor, Mahibullah, Manoshi; **GMC-4: Dr.-** Sadia, Riaz, Riya, Tahir, Rafa, Prema, Nur Ahmed, Sarwar, Zannatul Tanim, Hafisa, Sakib, Abhijit, Deborshi, Habib, Trisha, Abida sultana, Ashque, Tanjima, Rumman Tabassum, Rajib, Israt Jahan, Adnan Kamal, Shantanu Kar, Paksar, Raysa, Tima, Preema, Foysal, Proma, Alvee, Farhan, Falguni, Manjurul, Abir, Promiti, Hamza, Tuhin, Moon, Nirvana, Lipin, Farzana, Soumik, Jisan, Mila, Asif, Sifa, Hillol, Susanto, Hasib, Orpita, Subroto, Kanon, Tamanna, Zunayed, Masrur, Bablu, Irin, Mira, Tamanna, Puja, Natasa, Anika, Debolina, Nayeema, Nishat, Prince, Ayesha, Keya, Mushfiq, Habib, Hridoy, Rishat, Shuvo, Harun, Arman, Siam, Bijita, Karizma, Sifat, Sumaiya, Bushra, Pinki, Jerin, Susuma, Sufita, Habiba, Anonna, Kakoli, Koli, Atola; **GMC-08:** Tahmidul Haque Chowdhury; **GMC-9:** Avijit Ghosh, Sorna Akter Roji.

Anwar Khan Modern Medical College, Dhaka:
AKMMC-01: Dr.- Pabitra, Shovon, Sunny, Naim, Yousuf, Bari, Tayeef, Monzur; **AKMMC-02: Dr.-** Newaz, Kheya, Mili, Elahi, Aditi, Monodip, Lija, Sadia, Jinia, Aurin, Manar, Raju, Armin, John; **AKMMC-03: Dr.-** Ruponti, Labiba, Riad, Sinthia, Imran, Selim, Raja, Priyanka, Nahar, Robin, Sajib, Saiful, Oishee, Puja, Sahal, Suchi, Himel, Nuzhat, Maria; **AKMMC-04: Dr.-** Myth, Simul, Saraf, Sujon, Abir, Arpon, Nahid, Muna, Moutusi, Shorna, Muni, Tutfa, Sani, Mesba, Supti, Asif, Tisha, Kristi, Liza, Puja, Mounia, Munia, Samantha, Masuma, Shuvo, Oni, Minhaz, Priya, Nur, Saimon Sahariar, Punom, Ronti, Rehenuma; **AKMMC-09:** Tanvir Rashid Apurbo; **AKMMC-10:** Mahin Rahman Shetu, Musfika Tabassum, Prome, Anika, Fahmida, Mohsina, Rifat, Oasika, Abid, Safa.

Popular Medical College, Dhaka: PM-07: Rasel Babu.

Monno Medical College, Manikgonj: MoMC-1: Dr.- Dilruba Erani, Sabuz, Naim, Nur-A-Alam, Tanvir, Nahida, Mahmuda, Mithila, Sathi, Senjuti, Prince, Sayeful, Mahmud, Suman, Bappy, Dulal, Bristy, Jahid, Jui, Ashik, Al Amin, Mostafij, Nahid, Mifa, Saifullah, Darda, Mehedi, Borshon, Songita, Mukta, Swarna kar, Kaiser, Swarna, Foysal, Asad, Misty, Prova, Jhuma, Afsin, Tamanna, Saad, Jinath, Nowrin, Rifat, Rupa, Urmi, Jahan; **MoMC-2:** Bithi, Shahida, Tamim, Ela, Mim, Tasnim, Ashik, Ale, Saroar Don, Hridoy, Jony, Roman, Shihab, Alamgir, Morne, Bithi, Puja, Sajal, Sajib, Sourav, Swarnali, Wakil, Debika, Rayan, Hasib, Tushar, Lalin, Rajib, Tarik, Soikat, Linkon, Sopno, Lily, Foysal, Sohel, Nahid, Ashrafi, Mushnad, Rupon, Piya, Jubair, Jaba, Jothy, Majeda, Sadia, Rashed, Azad, Abdul Kader, Shohana, Sonia, Sohag, Liton, Sultan.

MH Shamorita Medical College, Dhaka: Humaira Arshi Hasan; **Batch-7:** Mymuna; **Batch-8:** Shanto.

Shaheed Monsur Ali Medical College, Dhaka:
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Shahabuddin Medical College, Dhaka: SM-15: Syeda Naeema Aziz, Hamidul Momen Choudhury.

Community Based Medical College: CB-23: Siam Sohanoor; **CB-24:** Farhana Afrin, Maimuna Fairose Mitu, Tahmina Rahman, Sudipto Das, Riado Sani, Ekramul Islam.

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Dr. Sirajul Islam Medical college: Session-17-18: Farhan Tanveer.

Aichi Medical College: AMC-02: Shimu Rani Sarker.

Universal Medical College: UMC-04: Raihanuzzaman Rishad.

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UNIT 03

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CHAPTER 01

BLOOD VESSEL

Diseases of Blood Vessels

Q. Mention the diseases of blood vessels.
Q. Mention the tumours of blood vessels. (CU-10Ju)
Q. Classify vascular tumours. (CMU-23/22/21/20M)
Ans.

Diseases of blood vessels: ***(Very Important for VIVA)***

1. **Congenital anomalies:**
   - Developmental or berry aneurysms
   - Arterio-venous fistula
   - Fibromascular dysplasia
   - Anomalous coronary artery origin
2. **Hypertensive vascular disease:**
   - Hypertension
     - Essential (primary) hypertension
     - Secondary hypertension
3. **Arteriosclerosis**
4. **Artherosclerosis**
5. **Aneurysms & dissection:**
   - Abdominal aortic aneurysm (AAA)
   - Thoracic aortic aneurysms
   - Aortic dissection
6. **Inflammatory disease- *vasculitis*:**
   - Infectious vasculitis
   - Non-infectious vasculitis
     - Wegner granulomatosis
     - Takayasu arteritis
     - Thromboangiitis obliterans (Buerger disease)
   - Giant cell (temporal) arteritis

- Kawasaki disease
- Polyarteritis nodosa (PAN)

7. **Raynaud phenomenon**

8. **Diseases of veins:**
   - Vericose veins
   - Thrombophlebitis & phlebothrombosis
   - Superior and inferior vena caval syndromes

9. **Diseases of lymphatics:**
   - Lymphangitis
   - Lymphedema

10. **Tumours and tumour like conditions:** ***(Very Important for VIVA)***
    a. **Benign tumours:**
       - ***Hemangioma:***
         - Capillary hemangioma
         - Cavernous hemangioma
         - Pyogenic granuloma
       - ***Lymphangiomas:***
         - Simple (capillary) lymphangioma
         - Cavernous lymphangioma (cystic hygroma)
       - ***Glomus tumour*** *(glomangioma)*
       - ***Vascular ectasias:***
         - Nevus flammeus
         - Spider telangiectasia (arterial spider)
         - Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)
       - ***Reactive vascular proliferations:***
         - Bacillary angiomatosis.

    b. **Intermediate-grade tumours:**
       - Kaposi sarcoma
       - Hemangioendothelioma

    c. **Malignant tumours:**
       - Angiosarcoma
       - Hemangiopericytoma.

(Ref: Robbins/10th/485,518)

Nice to Know:

Diseases of blood vessels: Two principal mechanisms underlie vascular disease:

(1) **Narrowing (stenosis)** or **complete obstruction** of vessel lumens, either progressively (e.g. by atherosclerosis) or precipitously (e.g. by thrombosis or embolism)

(2) **Weakening** of vessel walls, leading to dilation or rupture.

(Ref: Robbins/10th/485)

Vascular Structure and Function

All vessels except capillaries share a three-layered architecture consisting of an endothelium lined **intima**, a surrounding smooth muscle **media**, and supportive **adventitia**, admixed with extracellular matrix.

The ***intima*** normally consists of a single layer of endothelial cells sitting on a basement membrane which is demarcated from the media by the ***internal elastic lamina***.

The ***adventitia*** lies external to the media and in many arteries is separated from the media by a well-defined ***external elastic lamina.***
Capillaries are approximately the diameter of a red cell (7 to 8 μm); they have an ***endothelial cell lining*** but ***no media***, although variable numbers of ***pericytes***, cells that resemble smooth muscle cells, typically lie just deep to the the endothelium.

Arteries are divided into ***three types*** based on their size and structural features:

(1) ***Large*** or ***elastic arteries***, including the aorta, the major branches of the aorta (the innominate, subclavian, common carotid, and iliac arteries), and the pulmonary arteries;
(2) ***Medium sized*** or ***muscular arteries***, comprising smaller branches of the aorta (e.g., the coronary and renal arteries); and
(3) ***Small arteries*** (≤2 mm in diameter) and ***arterioles*** (20 to 100 μm in diameter), within tissues and organs.

Lymphatics are thin-walled channels lined by specialized endothelium; they provide conduits to return interstitial tissue fluid and inflammatory cells to the bloodstream.

(Ref: Robbins/10th/485)

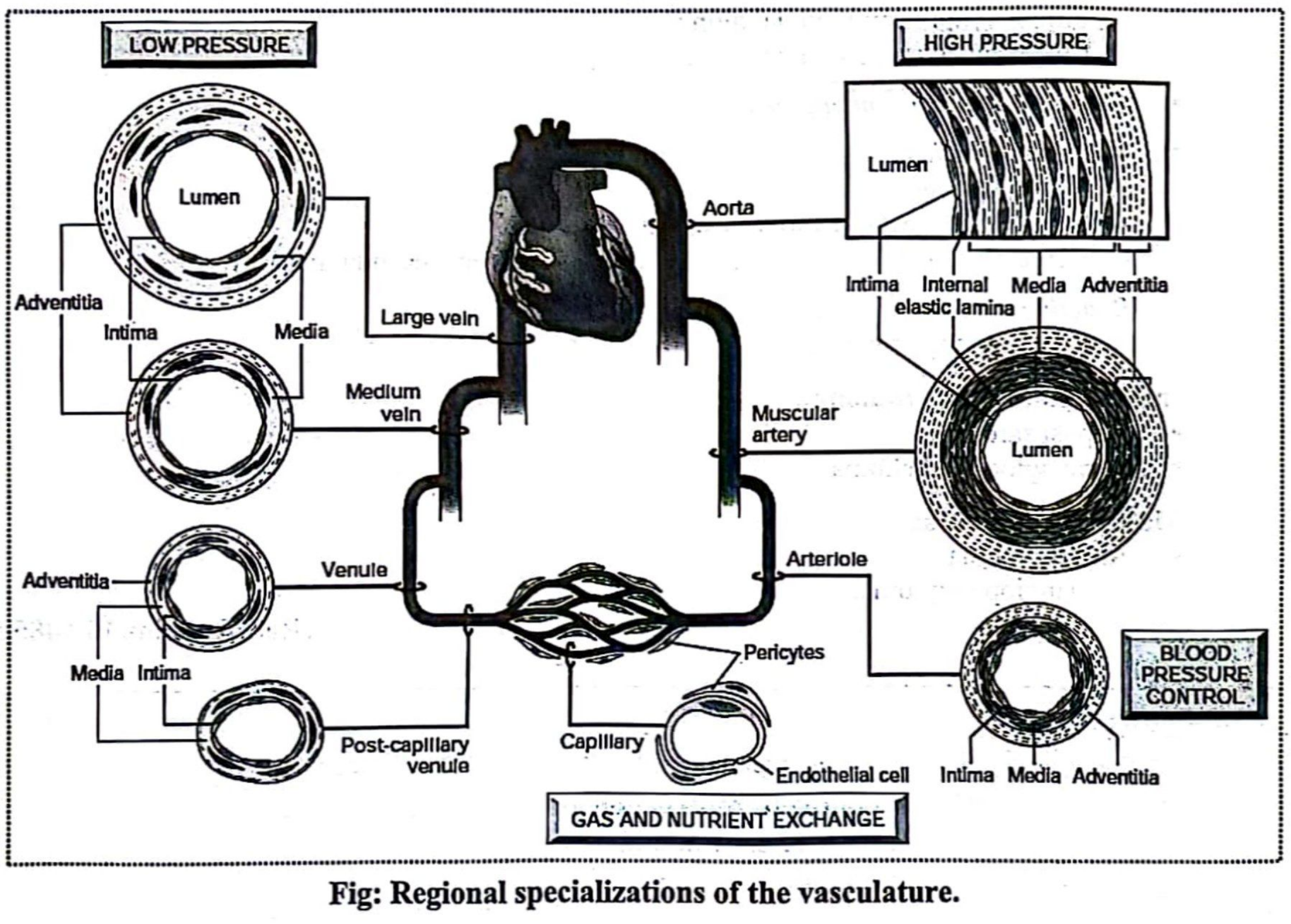


Fig: Regional specializations of the vasculature.

Congenital Anomalies of Blood Vessel

Q. What are the congenital anomalies of blood vessel? Describe any one of them.
Ans.
Congenital anomalies of blood vessel:

1. **Developmental or berry aneurysms** occur in cerebral vessels; when ruptured, these can cause fatal intracerebral hemorrhage.
2. **Arterio-venous fistulas** are direct connections (usually small) between arteries and veins that bypass capillaries.
3. **Fibromascular dysplasia** is a focal irregular thickening in medium and large muscular arteries including renal, carotid, splanchnic, and vertebral vessels.
4. **Anomalous coronary artery origin** occurs from a developmental anomaly in which both coronary arteries arise over the same coronary cusp of the aortic valve.

(Ref: Robbins/10th/487)

Arteriovenous fistulas: Arteriovenous fistulas are are direct connections (usually small) between arteries and veins that bypass capillaries.

Cause / etiology:

- Developmental defects
- Rupture of an arterial aneurysm into the adjacent vein
- Penetrating injuries that pierce arteries and veins
- Inflammatory necrosis of adjacent vessels
- Surgically generated arteriovenous fistulas (for hemodialysis)

Clinical importance:

- **Rupture**, leading to ***intracerebral hemorrhage***
- Large or multiple arteriovenous fistulas become clinically significant by shunting blood from the arterial to the venous circulations, forcing the heart to pump additional volume and leading to **high-output cardiac failure.**

(Ref: Robbins/10th/487)

Hypertension

Definition: According to the National Heart, Lung, and Blood Institute of the U.S.A, "A sustained diastolic pressure greater than 89 mm Hg, or a sustained systolic pressure in excess of 139 mm Hg is considered to constitute clinically significant hypertension.

(Ref: Robbins/10th/489)

Types of blood pressure in adults:

Category	Systolic (mm Hg)	Diastolic (mm Hg)
Normal	<130	<85
High normal	130 - 139	85 - 89
Hypertension:		
Mild	140 - 159	90-99
Moderate	160 -179	100 - 109
Severe	180 - 209	110 - 119
Very severe	>210	≥120

Types and causes of hypertension:

1. **Essential / Primary hypertension:** 90% - 95% of all cases.
2. **Secondary hypertension:**

Renal causes	▪ Acute glomerulonephritis ▪ Chronic renal disease ▪ Polycystic disease ▪ Renal artery stenosis ▪ Renal vasculitis

	▪ Renin-producing tumours
Endocrine causes	▪ Adrenocortical hyperfunction (Cushing syndrome, primary aldosteronism, congenital adrenal hyperplasia, licorice ingestion) ▪ Exogenous hormones (glucocorticoides, estrogens [including pregnancy-induced and oral contraceptives]) ▪ Pheochromocytoma ▪ Acromegaly ▪ Hypothyroidism (myxedema) ▪ Hyperthyroidism (thyrotoxicosis) ▪ Pregnancy-induced (preeclampsia)
Cardiovascular causes	▪ Coarctation of the aorta ▪ Polyarteritis nodosa ▪ Increased intravascular volume ▪ Increased cardiac output ▪ Rigidity of the aorta
Neurogenic causes	▪ Psychogenic ▪ Increased intracranial pressure ▪ Sleep apnoea ▪ Acute stress, including surgery

Ref: Robbins/10th/490)

Nice to Know:

Pheochromocytoma: It is a **catecholamine-secreting tumour of adrenal medulla.** So, it results in excessive formation of adrenaline and nor-adrenaline which causes increased blood pressure.

Q. Define malignant hypertension. *(Very Important for VIVA)*

Ans.

Malignant hypertension: Accelerated or ***malignant hypertension*** is a clinical syndrome characterized by **severe pressure elevations** (i.e. systolic pressure more than 200 mm Hg, diastolic pressure more than 120 mm Hg), **renal failure,** and **retinal hemorrhages** and **exudates,** with or without **papilledema** (swelling of the optic nerve that reflects increased intracranial pressures).

(Ref: Robbins/10th/490)

It can develop in previously normotensive persons but more often is superimposed on preexisting "benign" hypertension.

(Ref: Robbins/10th/490)

Q. What are the complications of hypertension?

Ans.

Complications of hypertension:

- Increasing risk of atherosclerosis
- Cardiac hypertrophy and heart failure (hypertensive heart disease)
- Myocardial infarction (heart attack)
- Multi-infarct dementia
- Aortic dissection
- Renal failure
- Cerebral hemorrhage (stroke)
- Hypertensive retinopathy
- Hypertensive encephalopathy.

(Ref: Robbins/10th/490)

Q. What are the causes of hypertension? (CU-18M)
Ans.
Causes of hypertension: *Please write from above discussion.*

Arteriosclerosis & Atherosclerosis

Q. Define and classify arteriosclerosis. (SU-14Ju) ***(Very Important for VIVA)***
Q. Short note: Arteriosclerosis. (DU-07Ja)
Ans.
Arteriosclerosis: Arteriosclerosis (literally means **"hardening of the arteries"**) is a generic term for **arterial wall thickening** and **loss of elasticity.**

(Ref: Robbins/10th/493)

Or,

Arteriosclerosis is a general term used to include all conditions with **thickening** and **hardening of the arterial walls.**

(Ref: Harsh Mohan/7th/371)

Classification: There are **four** general patterns, with different clinical and pathologic consequences.

1. **Arteriolosclerosis:** Affects small arteries and arterioles, and may cause downstream ***ischemic injury.*** The two anatomic variants are-
   - ***Hyaline arteriolosclerosis*** (characterized by *hyaline thickening* of arteriolar walls)
   - ***Hyperplastic arteriolosclerosis*** (characterized by *concentric, laminated, "onionskin" thickening* of arteriolar walls)
2. **Mönckeberg medial calcific sclerosis:** Characterized by **calcifications of the medial walls of muscular arteries,** typically starting along the internal elastic membrane. Adults older than age 50 are most commonly affected.
3. **Fibromuscular intimal hyperplasia:** It occurs in muscular arteries larger than arterioles. It is driven by inflammation (as in a healed arteritis or transplant-associated arteriopathy) or by mechanical injury (e.g. associated with stents or balloon angioplasty) and can be considered as a healing response.
4. **Atherosclerosis:** It is the most frequent and clinically important pattern characterized by intimal lesions called **fibrous plaques,** or **atheromas,** occur within the intima of arteries, most frequently the coronary arteries, cerebral arteries, large vessels of the lower extremities, and the renal and mesenteric arteries.

(Ref: Robbins/10th/493; BRS Pathology/5th/123)

Q. Define atherosclerosis (DU-22/18M,08Ju,07/05Ja, RU-21/20Nv, CU-12Ja) **and atheroma.** (CU-19Nv)
Q. Give the morphology of an atheromatous plaque. (DU-05M, SMU-23M,21Nv,19/18M, 15Ju,12/11Ja)
Q. What are the common sites and complications of atheromatous plaque? (DU-23Nv)
Q. Mention the histologic features of atherosclerosis. (RU-04Ja)
Q. Short note: Atherosclerosis. (DU-06Ja, RU-18M)
Q. Short note: Atheromatous plaque. (DU-17Nv)
Q. Short note: Atheroma. (RU-18Nv,13Ju, CU-15Ju)
Ans. ***(Very Important for VIVA)***
Atherosclerosis: Atherosclerosis is a pattern of **vascular disease** which is characterized by **intimal lesions** called **atheromas** (also called **atheromatous** or **atherosclerotic plaques**) that protrude into and **obstruct vascular lumen** and **weaken the underlying tunica media.**

(Ref: Robbins/10th/493 + 9th/491)

Or,

Atherosclerosis is an thickening and hardening of **large and medium-sized muscular arteries,** primarily due to involvement of **tunica intima** and is characterised by **fibrofatty plaques** or **atheromas.**

(Ref: Harsh Mohan/7th/373)

Atheroma / atherosclerotic plaque: A **fully developed atherosclerotic lesion** is called **atheromatous plaque,** also called ***fibrous plaque, fibrofatty plaque*** or ***atheroma.***

(Ref: Harsh Mohan/7th/378)

Common sites of formation of atheroma / atherosclerotic plaque: The blood vessels which are most extensively involved by atherosclerosis (in descending order) are:

1. Lower abdominal aorta and iliac arteries
2. Coronary arteries
3. Popliteal arteries
4. Internal carotid arteries
5. Vessels of the circle of Willis.

(Ref: Robbins/10th/501; BRS Pathology/5th/123)

Morphology of an atherosclerotic plaque: The key processes in atherosclerosis are **intimal thickening** and **lipid accumulation,** which together form **plaques.**

A) **Macroscopic:**

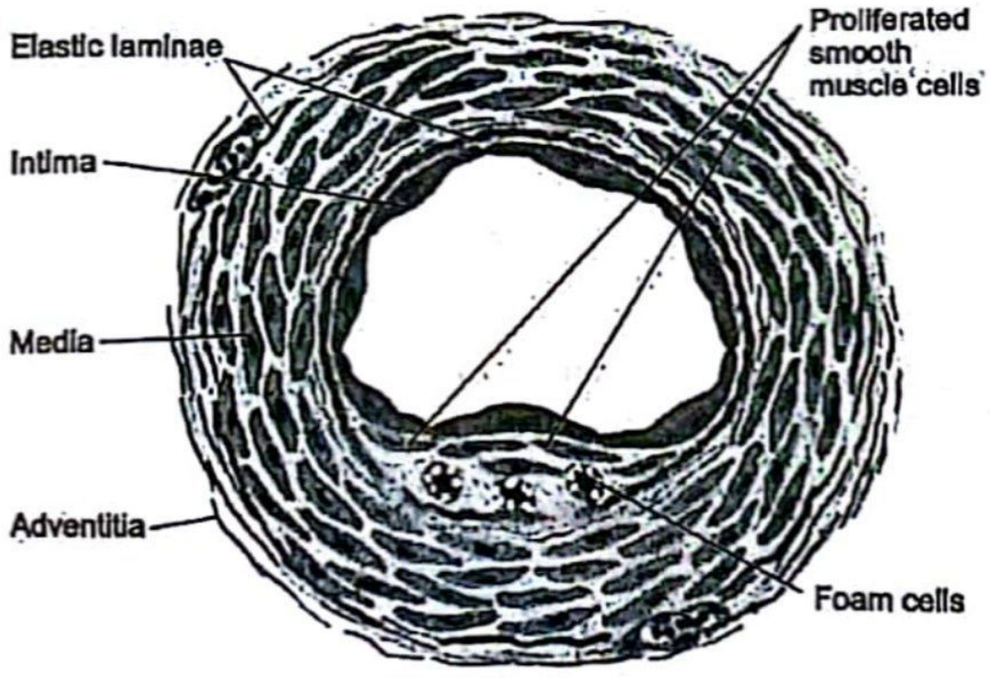
- **Colour: Yellow-tan** and are raised above the surrounding vessel wall; any superimposed thrombus over ulcerated plaques will be **red-brown.**
- **Size:** Plaques **vary in size** but can coalesce to form larger masses.
- **Shape:** Atherosclerotic lesions are **patchy** and **rarely circumferential,** usually involving only a portion of any given arterial wall; **on cross-section,** the lesions therefore appear **eccentric.**
- **Cut section:** The plaques have a **central (necrotic) core** covered by a subendothelial **fibrous cap:**
  1. **Superficial fibrous cap:** Composed of smooth muscle cells and relatively dense collagen.
  2. **Necrotic core:** Deep to the fibrous cap is a necrotic core containing lipid (primarily cholesterol and cholesterol esters), debris from dead cells, foam cells (lipid-laden macrophages and lipid-laden SMCs), fibrin, thrombus in varying degrees of organization, and other plasma proteins.
- **Periphery of the lesions: Neovascularization** (proliferating small blood vessels) present.

B) **Microscopic:** Atherosclerotic plaques have **four** principal components:

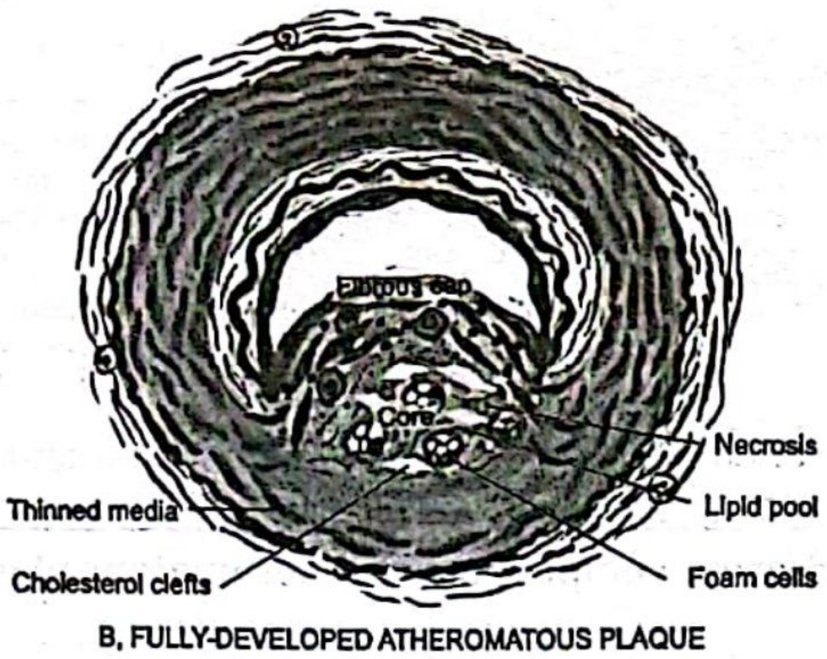
1. **Cells** including variable numbers of SMCs, macrophages, and T lymphocytes
2. **Extracellular matrix (ECM)** including collagen, elastic fibers, and proteoglycans
3. **Intracellular** and **extracellular lipids** (mostly cholesterol & cholesterol ester)
4. **Calcifications** (in later stage plaques).

Most atheromas contain abundant lipid, but some plaques (**"fibrous plaques"**) are composed almost exclusively of smooth muscle cells (SMCs) and fibrous tissue, which can be heavily calcified.

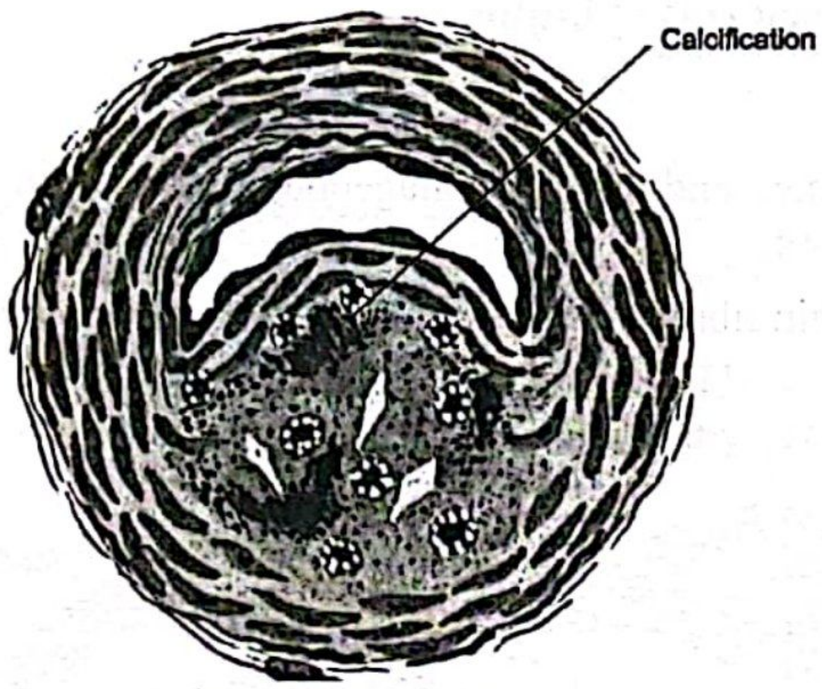
(Ref: Robbins/10th/499-502; BRS Pathology/5th/123; Harsh Mohan/7th/378)



A, EARLY LESION



B, FULLY-DEVELOPED ATHEROMATOUS PLAQUE



C, COMPLICATED PLAQUE

Fig: Schematic evolution of lesions in atherosclerosis.

Complications of atheromatous plaque:

1. Mechanical **obstruction** of blood flow.
2. Rupture of atherosclerotic plaques leading to **catastrophic obstructive vascular thrombosis.**
3. Atherosclerotic plaques can increase the diffusion distance from the lumen to the media, leading to ischemic injury and weakening of the vessel wall that can result in **aneurysm formation.**

(Ref: Robbins/10th/494)

Nice to Know:

The term **atherosclerosis** is derived from ***athero***-(meaning porridge) referring to the soft lipid-rich material in the centre of atheroma, and ***sclerosis*** (scarring)-referring to connective tissue in the plaques. It is the commonest and the most important of the arterial diseases.

(Ref: Harsh Mohan/7th/373)

Q. Draw and label typical atheroma. (DU-23Nv)

Q. Draw and label the different components of atheromatous plaque. (DU-07Ja)

Ans.

Different components of atheromatous plaque:

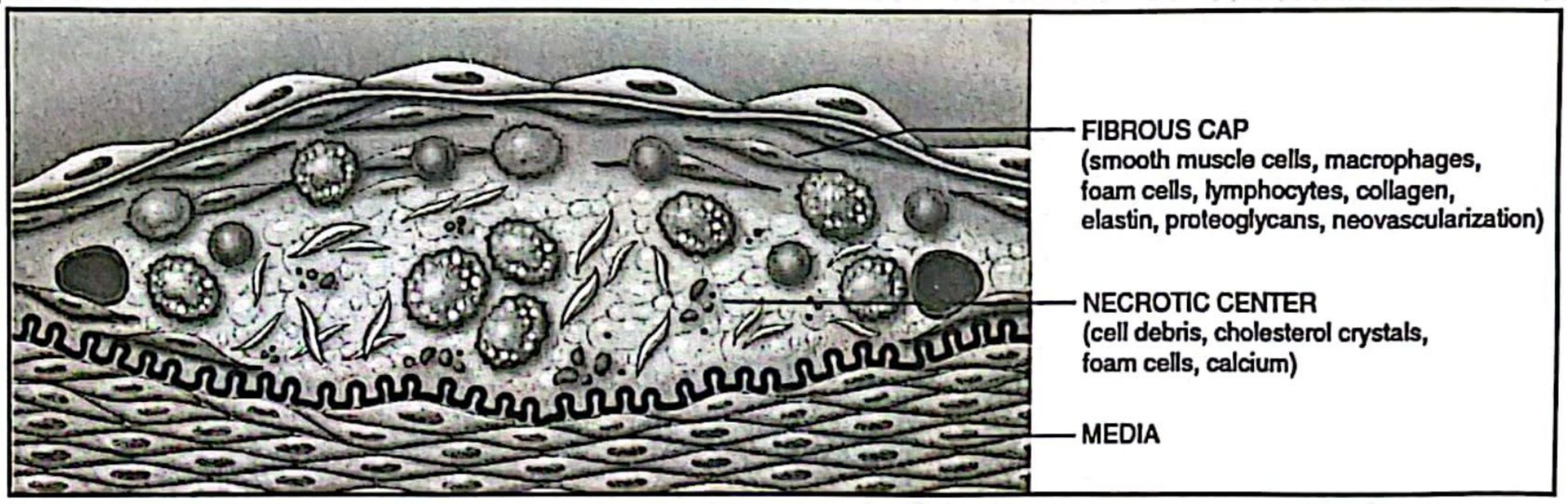

FIBROUS CAP
(smooth muscle cells, macrophages, foam cells, lymphocytes, collagen, elastin, proteoglycans, neovascularization)
NECROTIC CENTER
(cell debris, cholesterol crystals, foam cells, calcium)
MEDIA

Fig: Different components of atheromatous plaque.

(Ref: Robbins/10th/494)

Q. Mention the types of atherosclerotic plaque.

Ans.

Types of atherosclerotic plaque:

1. ***Stable plaques*** have thickened and densely collagenous fibrous caps with minimal inflammation and underlying atheromatous core.
2. ***Vulnerable plaques*** have thin fibrous caps, large lipid cores, and increased inflammation.

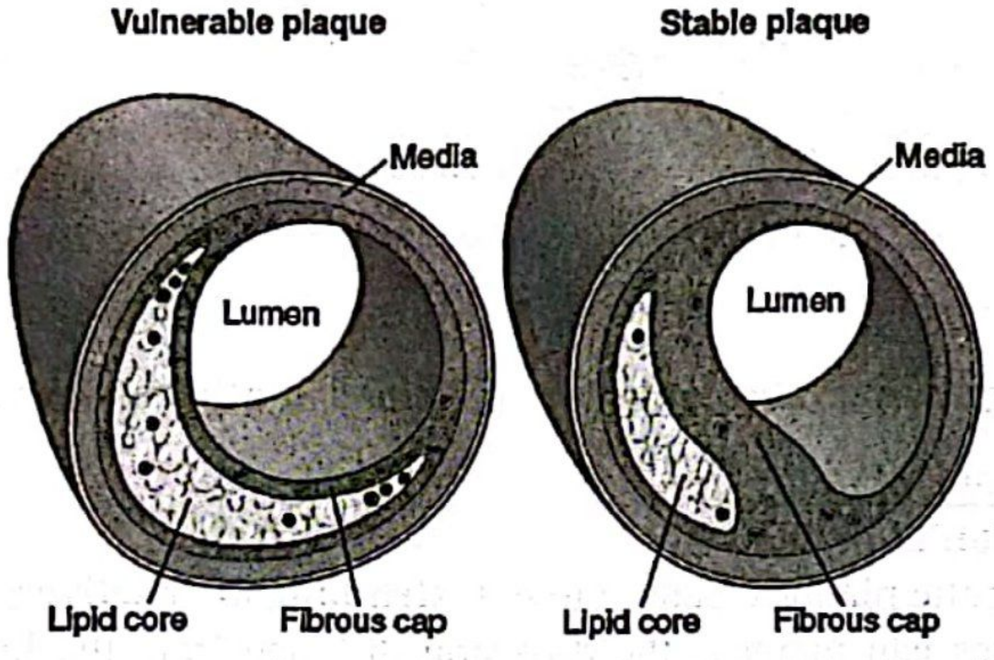


Fig: Vulnerable and stable atherosclerotic plaque.

(Ref: Robbins/10th/503)

Q. What is the difference between arteriosclerosis and atherosclerosis? *(Very Important for VIVA)*

Ans.

Difference between arteriosclerosis and atherosclerosis: Arteriosclerosis (literally means **"hardening of the arteries"**) is a generic term for **arterial wall thickening** and **loss of elasticity**. On the other hand, atherosclerosis is the most frequent and clinically important ***variety of arteriosclerosis*** which is characterized by **formation of intimal lesions** called **atheromas** (also called **atheromatous** or **atherosclerotic plaques**) that protrude into and obstruct vascular lumen and weaken the underlying tunica media.

(Ref: Robbins/10th/493)

Q. What is foam cell? *(Very Important for VIVA)*

Ans.

Foam cell: Foam cells are **lipid-laden macrophages** and **lipid-laden smooth muscle cells.**

(Ref: Robbins/10th/501; BRS Pathology/5th/123)

Q. What is 'fatty streak'? Mention its significance.

Ans.

Fatty streaks: Fatty streaks are lesions composed primarily of **lipid-filled foamy macrophages**. Beginning as small flat yellow macules, these can eventually coalesce into elongated streaks 1 cm long or longer.

(Ref: Robbins/10th/499)

Or,

Fatty streaks are lesions lying **under the endothelium** and are composed of **closely-packed foam cells**, lipid-containing elongated **smooth muscle cells** and a few **lymphoid cells**. Small amount of extracellular lipid, collagen and proteoglycans are also present.

(Ref: Harsh Mohan/7th/377)

They are especially prominent in the **aorta** and other **major arteries**, more often on the **posterior wall** than the anterior wall.

Significance:

- The lesions are not particularly raised and do not cause any significant flow disturbance.
- Fatty streaks on the intima by themselves are harmless but may be the precursor lesions of atheromatous plaques.

(Ref: Robbins/10th/499; BRS Pathology/5th/124; Harsh Mohan/7th/378)

Q. Mention the risk factors of atherosclerosis. (DU-18/17M,08Ju,05Ja, SMU-23M,22Nv/M,21Nv, 19/18/17M,15Ju,12/11Ja, BUP-22M, RU-20/19Nv,18Ja,15/14/12Ju, CU-20Ju)
Q. Write the major risk factors of atherosclerosis. (DU-22M)
Q. Mention four important risk factors of atherosclerosis. (DU-07Ju)
Q. Mention four preventable risk factors for atherosclerosis. (SU-12Ju)
Ans.

Risk factors for atherosclerosis: ***(Very Important for VIVA)***

Major risk factors:

Non-modifiable (constitutional):

1. Genetic abnormalities
2. Family history
3. Increasing age
4. Male gender

Modifiable (potentially controllable):

1. Hyperlipidaemia (more specifically hypercholesterolemia)
2. Hypertension
3. Cigarette smoking
4. Diabetes

Additional risk factors:

1. Inflammation & evevated C-reactive protein (CRP)
2. Hyperhomocystinemia
3. Metabolic syndrome
4. Lipoprotein a [Lp(a)]
5. Factors affecting hemostasis (Prothrombotic factors and elevated fibrinogen levels)
6. Other factors
   - Obesity
   - Lack of exercise / physical inactivity
   - High carbohydrate intake
   - Competitive, stressful lifestyle (type A personality)

(Ref: Robbins/10th/494; BRS Pathology/5th/124; Harsh Mohan/7th/373)

(***N.B*: Obesity** also being complicated by hypertension, diabetes, hypertriglyceridemia, and decreased HDL).

(Ref: Robbins/10th/497)

Nice to Know:

Description of some of the important risk factors:

1. **Genetics: Family history** is the **most important** independent risk factor for atherosclerosis. Certain Mendelian disorders are strongly associated with atherosclerosis (e.g. familial hypercholesterolemia), but these account for only a small percentage of cases.
2. **Age:** Atherosclerosis is an age-related disease. Its incidence **increases with age**. Fully-developed atheromatous plaques usually become clinically manifested in **middle age or later** (40 - 60 years).
3. **Gender:** Atherosclerosis is **more common in men** in all age groups, although the incidence increases in **postmenopausal women.**
4. **Hyperlipidemia:**
   - Hyperlipidemia and more specifically **hypercholesterolemia**-is a major risk factor for atherosclerosis; even in the absence of other risk factors, hypercholesterolemia is sufficient to initiate lesion development.
   - Atherosclerosis is **directly proportional** to **increase LDL**, also known as **"bad cholesterol"** and **decrease HDL**, also known as **"good cholesterol"**.
5. **Hypertension:** It is a major risk factor, and is associated with, premature atherosclerosis. It increases the risk of IHD by approximately 60%.
6. **Diabetes mellitus:**
   - It **induces hypercholesterolemia** and markedly increases the risk of atherosclerosis.
   - Atherosclerotic **peripheral vascular occlusive disease,** often leading to **gangrene of the lower extremities,** is common in diabetic patients.
   - The incidence of myocardial infarction (MI) is twice as high in diabetics as in non-diabetics.
7. **Metabolic syndrome:** It is characterized by **insulin resistance, hypertension, dyslipidemia** (elevated LDL and depressed HDL), **hypercoagulability,** and a **proinflammatory state.**

(Ref: Robbins/10th/494; Harsh Mohan/7th/373)

Q. Give the etio-pathogenesis of atherosclerosis. (CU-14Ju) ***(Very Important for VIVA)***
Q. State the pathogenesis of atherosclerosis. (DU-22M, CMU-21/20Nv,19/18M,10Ju, RMU-21Nv,19M,14/12/11Ju, SU-12Ju,06M)
Q. Write down the mechanism / pathogenesis of formation of an atheromatous plaque. (BUP-22M, CU-16Ju/Ja,13Ju,12Ja)
Q. How atheroma is formed? (CU-18Nv)
Ans.
Pathogenesis of atherosclerosis: Atherosclerosis progresses in the following sequence:

1. **Endothelial injury and dysfunction,** causing (among other things) increased vascular permeability, leukocyte adhesion, and thrombosis
2. **Accumulation of lipoproteins** (mainly LDL and its oxidized forms) in the vessel wall
3. **Monocyte adhesion to the endothelium,** followed by migration into the intima and transformation into *macrophages* and *foam cells*
4. **Platelet adhesion**
5. **Factor release** from activated platelets, macrophages, and vascular wall cells, including *smooth muscle cell recruitment*, either from the media or from circulating precursors
6. **Smooth muscle cell proliferation, extracellular matrix production,** and **recruitment of T-cells**
7. **Lipid accumulation** both extracellularly and within cells (macrophages and smooth muscle cells)
8. **Calcification** of ECM and necrotic debris late in the pathogenesis.

(Ref: Robbins/10th/497)

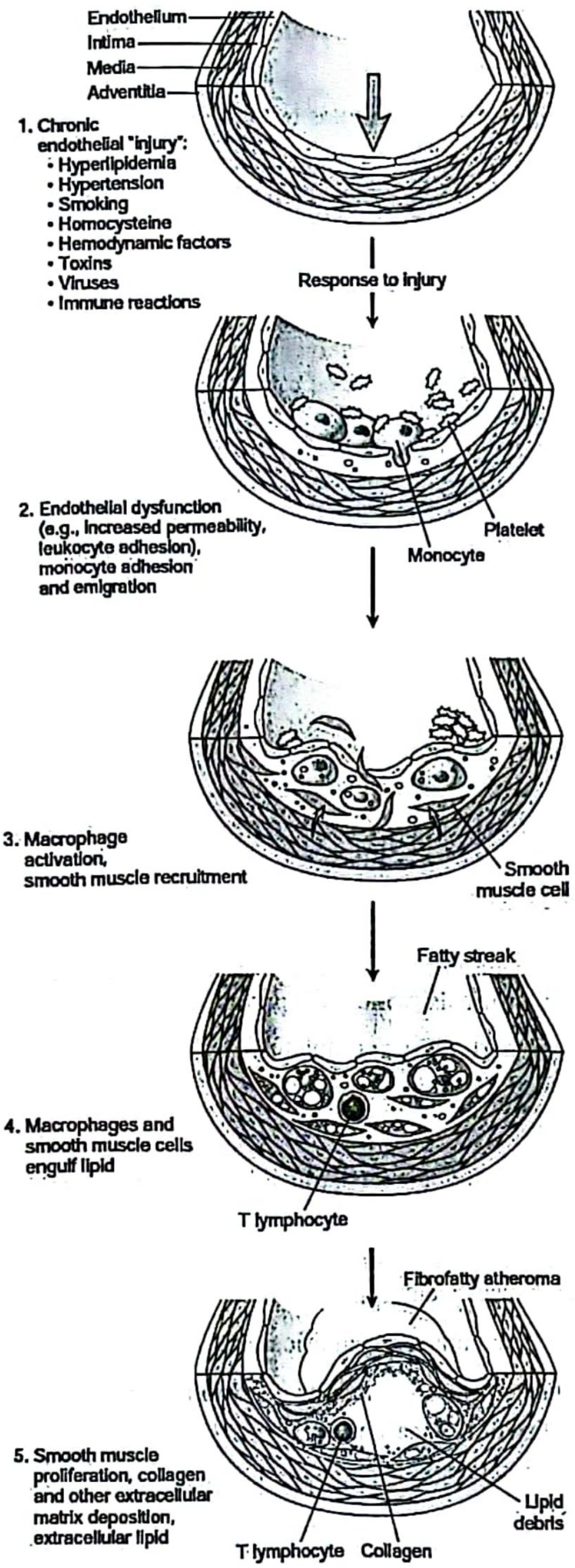


Fig: Pathogenesis of atherosclerosis.

Q. Mention the role of lipids in the pathogenesis of atherosclerosis.

Ans.

Role of lipids in the pathogenesis of atherosclerosis: Hyperlipidemia may initiate endothelial injury, promote foam cell formation, act as a chemotactic factor for monocytes, inhibit macrophage motility, or injure smooth muscle cells.

The mechanisms by which hyperlipidemia contributes to atherogenesis include the following:

A. **Impaired endothelial cell (EC) function:** Chronic hyperlipidemia (particularly hypercholesterolemia) can directly impair endothelial cell function by **increasing local reactive oxygen species production**; besides causing membrane and mitochondrial damage, oxygen free radicals accelerate NO decay, dampening its vasodilator activity.

B. **Modified LDL:**
   - With chronic hyperlipidemia, **lipoproteins accumulate within the intima**, where they may aggregate or become **oxidized** by free radicals produced by inflammatory cells.
   - These **modified lipoproteins (oxidized LDLs)** are ingested by **macrophages** and **smooth muscle cells** but cannot be completely degraded; chronic ingestion leads to the formation of **lipid-laden macrophages** called **foam cells.** The early lesions containing lipid-filled macrophages are called ***fatty streaks***.
   - Modified lipoproteins (**oxidized LDLs**) are toxic to endothelial cells, smooth muscle cells and macrophages, and can induce endothelial cell dysfunction.
   - Modified lipoproteins (**oxidized LDLs**) also stimulate the release of growth factors, cytokines, and chemokines that create a vicious **inflammatory cycle** of monocyte recruitment and activation.

(Ref: Robbins/10th/498; BRS Pathology/5th/125)

Q. Mention the complications of atherosclerosis. (DU-17M,06S,05Ja, RU-03Ja)
Q. Discuss briefly the complications of atherosclerosis. (DU-07Ju)
Q. Mention the effects of atherosclerosis. ***(Very Important for VIVA)***
Ans.

Effects / complications of atherosclerosis: Atherosclerotic plaques are susceptible to following clinically important changes-

1. **Rupture, ulceration, or erosion** of the surface of atheromatous plaques exposes highly thrombogenic substances and leads to **thrombosis**, which can partially or completely occlude the vessel lumen.
2. **Ischemia:** Thrombosis can partially or completely occlude the vessel lumen resulting in acute tissue infarction (e.g. myocardial or cerebral infarction).
3. **Hemorrhage** into a plaque.
4. **Atheroembolism:** Plaque rupture can discharge atherosclerotic debris into the bloodstream, producing microemboli.
5. **Aneurysm formation:** Atherosclerosis-induced pressure or ischemic atrophy of the underlying media, with loss of elastic tissue, causes weakness and potential rupture.
6. **Calcification:** Atheromas often undergo calcification.
7. **Infarction:** Ischemia induced infarction results in various organs due to atherosclerotic plaque-
   - ***Heart:*** Myocardial infarction (Heart attack).
   - ***Brain:*** Cerebral infarction (stroke).
   - ***Aorta:*** Aortic aneurysms.
   - ***Small intestine:*** Ischaemic bowel disease, infarction.
   - ***Peripheral vessels:*** Peripheral vascular disease (gangrene of the legs).
8. **Complication due to atherosclerotic stenosis** (*Gradual occlusion of vessel lumen*)**:**
   - Mesenteric occlusion & bowel ischemia
   - Sudden cardiac death
   - Chronic ischemic heart disease (IHD)

- Ischemic encephalopathy
- Intermittent claudication (diminished perfusion of the extremities).

(Ref: Robbins/10th/502; Harsh Mohan/7th/381)

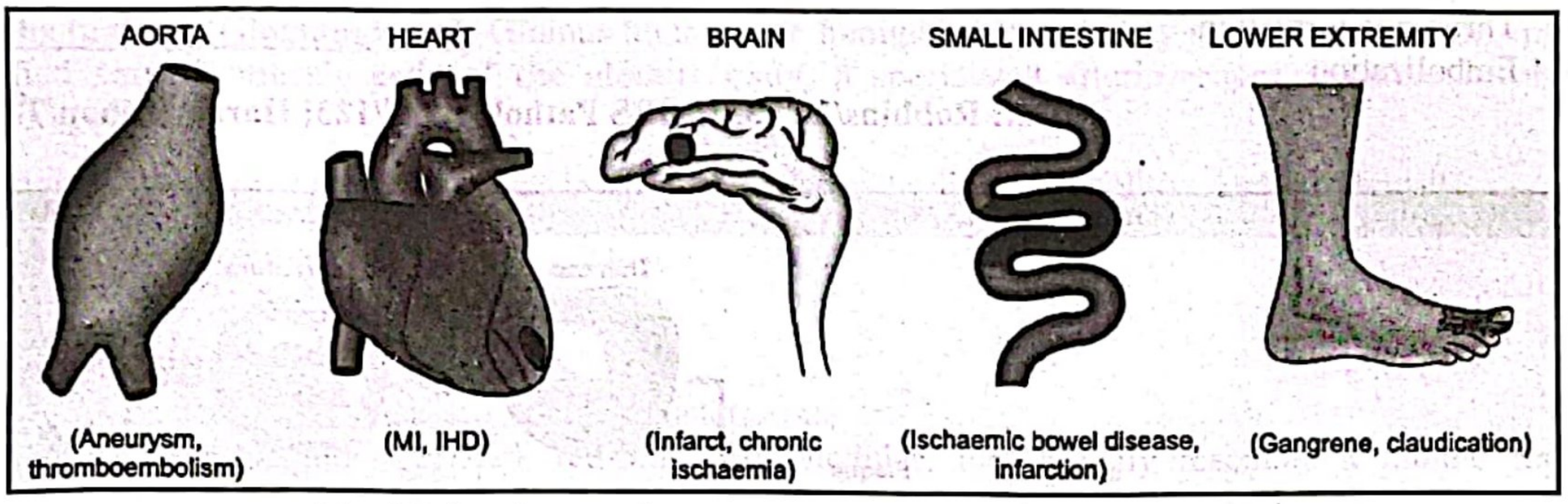


Fig: Major forms of symptomatic atherosclerotic disease.

Q. Name the blood vessels which are more frequently involved by atherosclerosis with their possible clinical consequences. (DU-18M)

Q. Mention the major consequences of atherosclerosis in different organs. *(Very Important for VIVA)*

Ans.

<u>Blood vessels frequently involved by atherosclerosis with their possible clinical consequences</u>:

1. **Coronary arteries:** Ischemic heart disease and myocardial infarction (heart attack).
2. **Larger branches of the carotid arteries & the circle of Willis:** Stroke from cerebral ischemia & infarction.
3. **Large vessels of the lower extremities** (e.g. popliteal arteries)**:** Peripheral vascular occlusive disease with findings varying from claudication to ischemic necrosis and gangrene.
4. **Aorta:** Aortic aneurysms.
5. **Renal arteries:** Renal arterial ischemia with secondary hypertension.
6. **Mesenteric arteries:** Ischaemic bowel disease, infarction.

(Ref: Robbins/9th/498; BRS Pathology/5th/123,124; Harsh Mohan/7th/381)

Q. Mention the clinical consequences of atherosclerotic disease. *(Important for VIVA)*

Ans.

<u>Clinical consequences of atherosclerotic disease</u>:

1. **Major consequences:** Symptomatic atherosclerotic disease most often involves the arteries supplying the heart, brain, kidneys and lower extremities. The major consequences of atherosclerosis are-
   - Myocardial infarction (heart attack)
   - Cerebral infarction (stroke)
   - Aortic aneurisms
   - Ischaemic bowel disease & infarction.
   - Peripheral vascular disease (gangrene of the legs)
2. **Consequences due to atherosclerotic stenosis:** Gradual occlusion of vessel lumen results in-
   - Mesenteric occlusion & bowel ischemia
   - Sudden cardiac death
   - Chronic ischemic heart disease (IHD)
   - Ischemic encephalopathy
   - Intermittent claudication (diminished perfusion of the extremities).

3. Consequences due to acute plaque change:

- Plaque rupture / fissuring
- Plaque erosion / ulceration
- Plaque hemorrhage
- Thrombus formation
- Embolization.

(Ref: Robbins/10th/502; BRS Pathology/5th/123; Harsh Mohan/7th/389)

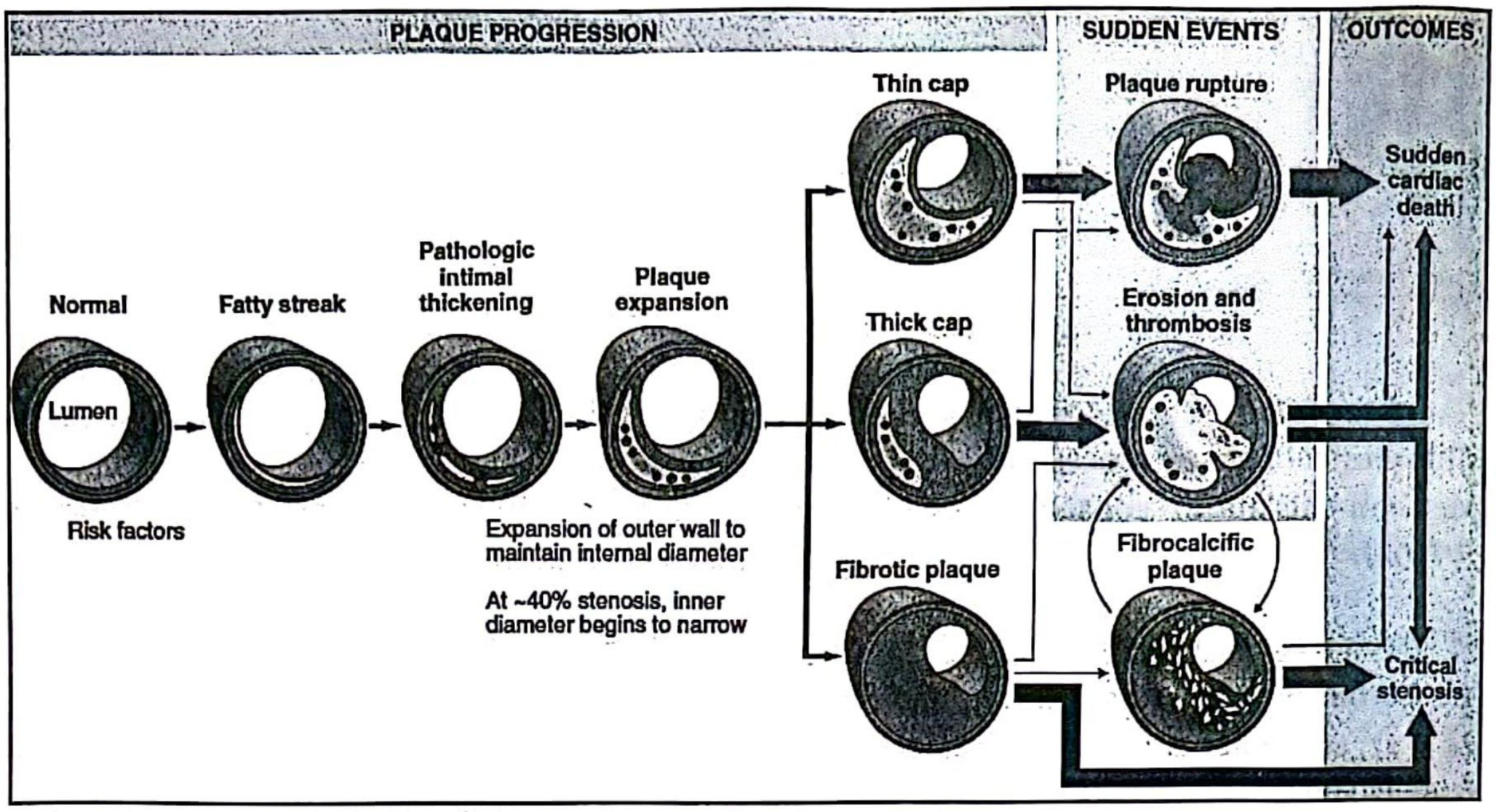


Fig: Atherosclerotic plaque formation, activities, and outcomes.

Q. What are the major targets of atherosclerosis? *(For VIVA)*

Ans.

Major targets of atherosclerosis:

- **Large elastic arteries** (e.g. aorta, carotid, and iliac arteries)
- **Large and medium-sized muscular arteries** (e.g. coronary and popliteal arteries).

(Ref: Robbins/10th/502)

Q. Write about the prevention of atherosclerosis.

Ans.

Prevention of atherosclerosis:

1. **Primary prevention:**
   - Cessation of cigarette smoking
   - Control of hypertension
   - Weight reduction
   - Increase exercise
   - Moderation of alcohol consumption
   - Lowering total and LDL blood cholesterol levels while increasing HDL.
2. **Secondary prevention:** Prevent recurrence of events such as MI in patients with symptomatic disease.

(Ref: Robbins/10th/494)

Vascular Tumours

Q. Short note: Glomus tumour.

Ans.

Glomus tumour (Glomangioma): Glomus tumours are **benign** but **exquisitely painful** tumours arising from **modified smooth muscle cells of the glomus body,** a specialized arterio-venous structure involved in thermoregulation.

Location: They are most commonly found in the distal portion of the digits, especially under the fingernails.

Treatment: Excision is curative.

Morphology:

***Grossly*:**

- Tumours are usually < 1 cm in diameter.
- Round, slightly elevated, red-blue, firm nodules, that initially resemble a minute focus of haemorrhage.

***Histologically*:**

- These are aggregates, nests, and masses of specialized glomus cells associated with branching vascular channels, all within a connective tissue stroma.
- Individual tumour cells are usually small, uniform, and round or cuboidal, with scant cytoplasm and ultra-structural features are very similar to smooth muscle cells.

(Ref: Robbins/10th/520)

Q. What is haemangioma? Write about capillary haemangioma.

Ans.

Haemangioma: Haemangiomas are **benign neoplasm of the blood vessels.** They are very common tumors composed of blood-filled vessels.

(Ref: Robbins/10th/519)

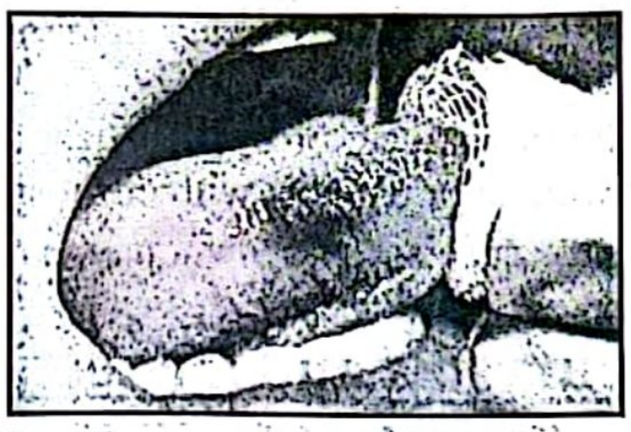


Fig: Haemangioma of the tongue.

Age: Infancy and childhood (7% of all benign tumors of this age).

Types:

1. Capillary hemangiomas
2. Juvenile hemangiomas (so-called "strawberry type" hemangiomas)
3. Cavernous hemangioma
4. Pyogenic granulomas.

Capillary hemangioma: They are the ***most common type*** that consists of a tangle of closely packed capillary-like channels, and occur in the skin, subcutaneous tissues, and mucous membranes of the oral cavities and lips, as well as in the liver, spleen, and kidneys.

Morphology:

- Bright red to blue
- Few millimeters to several centimeters in diameter

- At level with the surface of the skin or slightly elevated
- Intact overlying epithelium

Histologically:

- Unencapsulated aggregates of **closely packed, thin-walled capillaries**, usually blood-filled and lined by flattened endothelium
- Vessels are separated by **scant** connective tissue **stroma**
- The lumens may be partially or completely thrombosed and organized
- Hemosiderin pigment due to vessel rupture
- Focal scarring.

(Ref: Robbins/10th/519 + 9th/516 + 8th/520)

Q. What is lymphangioma? *(For VIVA)*

Ans.

Lymphangiomas: Lymphangiomas are the benign lymphatic counterparts of hemangiomas.

Types:

1. Simple (capillary) lymphangioma
2. Cavernous lymphangioma (cystic hygroma).

(Ref: Robbins/10th/520)

Q. What is angiosarcoma? *(For VIVA)*

Ans.

Angiosarcoma: Angiosarcoma is the **malignant endothelial neoplasm** of the blood vessel.

(Ref: Robbins/10th/522)

Q. What is spider telangiectasia? Where it commonly seen? *(For VIVA)*

Ans.

Spider telangiectasia: Spider telangiectasias are **non-neoplastic vascular malformations** grossly resembling a **spider**. These manifest as radial, often pulsatile lesions composed of ***dilated subcutaneous arteries or arterioles*** (resembling **spider legs**) about a ***central core*** (resembling a **spider's body**) that blanch with pressure.

Location: These commonly occur on the **face, neck,** or **upper chest** and are most frequently associated with hyperestrogenic states (e.g. in pregnant women or patients with cirrhosis).

(Ref: Robbins/10th/519)

Aneurysms and Dissections

(Important for VIVA)

- **Aneurysm:** An aneurysm is a **localized abnormal dilation of a blood vessel or the heart** that may be congenital or acquired. When it involves the aorta, it is called **aortic aneurysm.**

  True aneurysm: When an aneurysm involves all the layers of an intact (but attenuated) arterial wall or the thinned ventricular wall of the heart, it is called a **true aneurysm.**

  Atherosclerotic and congenital vascular aneurysms and ventricular aneurysms that follow transmural myocardial infarctions are of this type.

  False aneurysm: A **false aneurysm** (also called a **pseudoaneurysm**) is a defect in the vascular wall leading to an extravascular hematoma that freely communicates with the intravascular space ("pulsating hematoma").

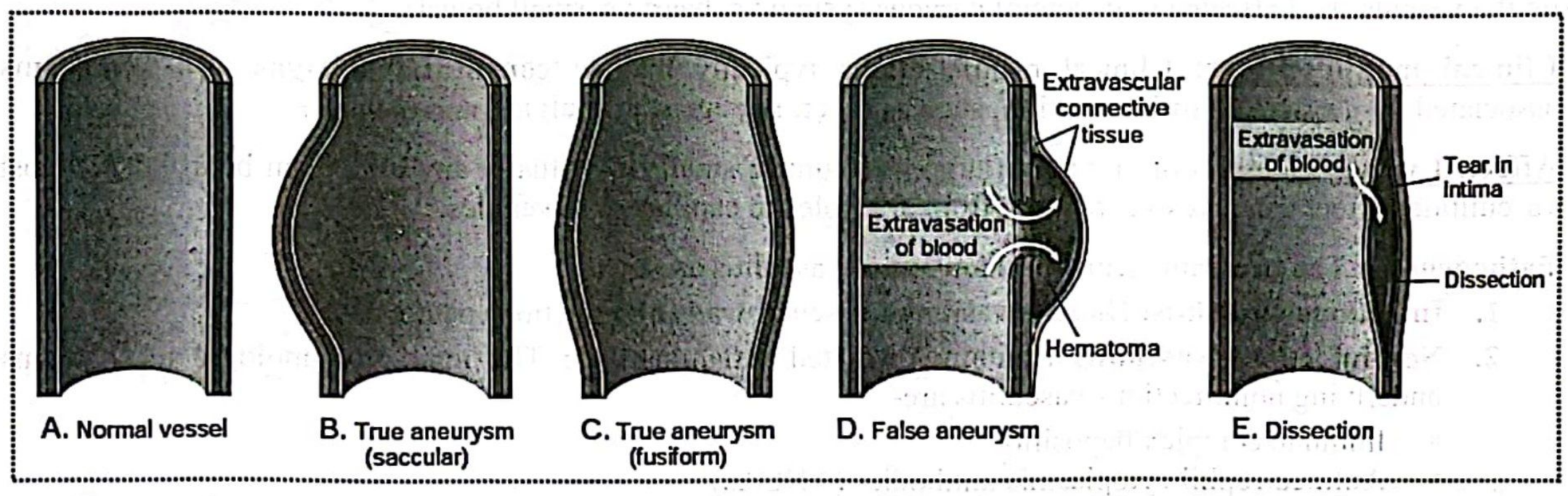
  Examples include a ventricular rupture after myocardial infarction that is contained by a pericardial adhesion or a leak at the sutured junction of a vascular graft with a natural artery.

  (Ref: Robbins/10th/504)

Classification of aneurysm: Aneurysms are classified by macroscopic shape and size-

1. ***Saccular aneurysms*** are essentially spherical outpouchings (involving only a portion of the vessel wall).
2. ***Fusiform aneurysms*** involve diffuse, circumferential dilation of a long vascular segment.

(Ref: Robbins/10th/505)



Causes of aneurysm:

1. Atherosclerosis
2. Hypertension
3. Advanced age
4. Smoking
5. Trauma
6. Vasculitis
7. Congenital defects (e.g. fibromuscular dysplasia and berry aneurysms typically in the circle of Willis)
8. Infections (mycotic aneurysms).

(Ref: Robbins/10th/506)

- **Arterial dissection:** An arterial dissection arises when blood enters a defect in the arterial wall and tunnels through medial or medial-adventitial planes. Dissections are often, but not always, aneurismal.

  Both true and false aneurysms as well as dissections can **rupture**, often with **catastrophic consequences.**

  (Ref: Robbins/10th/505)

- **Aortic dissection:** Aortic dissection occurs when blood separates the laminar planes of the media to form a blood-filled channel within the aortic wall.

  Aortic dissection is generally associated with aortic dilation; it can be disastrous if the dissection then ruptures through the adventitia and hemorrhages into adjacent spaces.

  Aortic dissection occurs principally in two groups of patients:
  (1) Men aged 40 to 60 years, with antecedent hypertension (more than 90% of cases)
  (2) Younger patients with syndromic diseases affecting the aorta (e.g. Marfan syndrome).

  Hypertension is the major risk factor for aortic dissection.

  Clinical features: The classic clinical symptoms of aortic dissection are the sudden onset of excruciating pain, usually beginning in the anterior chest, radiating to the back between the scapulae, and moving downward as the dissection progresses; the pain can be confused with that of myocardial infarction.

  The most common cause of death is rupture of the dissection and bleeding into the pericardial, pleural, or peritoneal cavities.

  (Ref: Robbins/10th/507)

Vasculitis

(Important for VIVA)

Vasculitis: *Vasculitis* is a general term for **vessel wall inflammation** with protean manifestations depending on the vascular bed affected (e.g. central nervous system vs. heart vs. small bowel).

Clinical manifestations: Clinical manifestations typically include **constitutional signs and symptoms** associated with **systemic inflammation**, such as fever, myalgias, arthralgias, and malaise.

Affected vessels: Vessels of any type (large, medium & small) in virtually any organ can be affected; most vasculitides affect small vessels ranging from arterioles to capillaries to venules.

Pathogenesis: The two pathogenic mechanisms of vasculitis are-

1. **Infectious vasculitis:** Direct invasion of vascular walls by infectious pathogens.
2. **Non-infectious vasculitis** (immune-mediated inflammation)**:** The main immunologic mechanisms underlying noninfectious vasculitis are-
   - Immune complex deposition
   - Antineutrophil cytoplasmic antibodies (ANCAs)
   - Anti-EC antibodies
   - Autoreactive T cells.

Types of vasculitis with their causes & example:

Vasculitis type	Examples
Non-infectious vasculitis (Immunologic)	
Immune complex mediated	▪ Infection-induced (e.g. hepatitis B & C virus) ▪ Henoch-Schonlein purpura ▪ SLE and rheumatoid arthritis ▪ Drug-induced ▪ Cryoglobinaemia ▪ Serum sickness ▪ Arthus phenomenon
Anti-neutrophil cytoplasmic antibody (ANCA) mediated	▪ Wegner granulomatosis ▪ Microscopic polyangiitis (microscopic polyarteritis) ▪ Churg-strauss syndrome
Direct antibody mediated	▪ Goodpasture syndrome (anti-GBM antibodies) ▪ Kawasaki disease (anti-endothelial cell antibodies)
Autoreactive T-cell mediated	▪ Organ allograft rejection
Inflammatory bowel disease. ***Paraneoplastic vasculitis***	
Infectious vasculitis (Direct infection)	
Bacterial	e.g. *Neisseria*
Rickettsial	Rocky Mountain spotted fever
Spirochetal	Syphilis
Fungal	Aspergillosis, mucormycosis
Viral	Herpes zoster, varicella
Unknown	
	▪ Giant cell (temporal) arteritis ▪ Takayasu arteritis ▪ Polyarteritis nodosa (PAN)

(Ref: Robbins/10th/508-516)

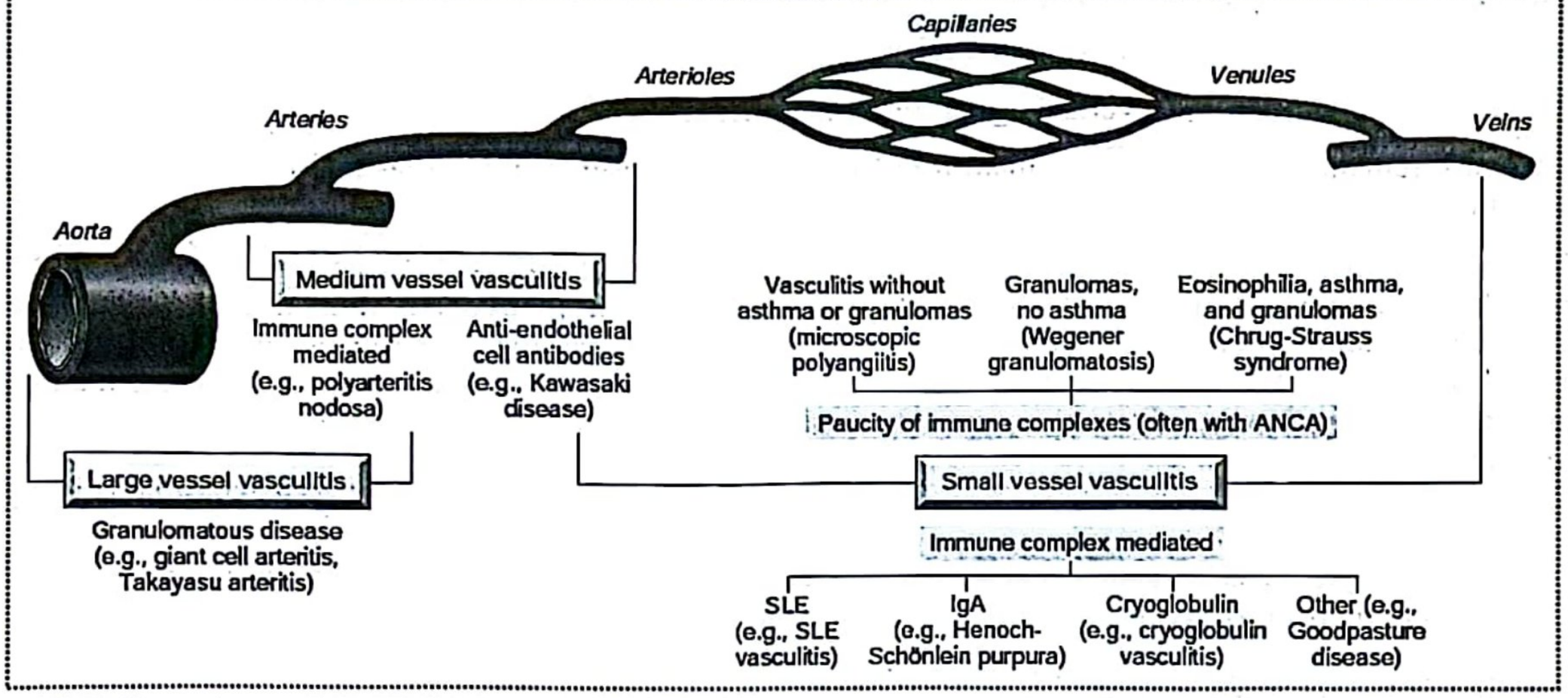


Fig: Vascular sites typically involved with the more common forms of vasculitis, as well as their presumptive etiologies.

Some Important Topics for VIVA

Giant cell (temporal) arteritis: Giant cell (temporal) arteritis is a **chronic,** classically **granulomatous inflammation** of **large- to small-sized arteries.**

Temporal arteritis is the most common form of vasculitis among elderly adults. It is rare before age 50. It principally affects **arteries in the head. Vertebral** and **ophthalmic arteries,** as well as the **aorta** (***giant cell aortitis***), also can be involved. Ophthalmic artery involvement can lead to **sudden** and **permanent blindness.**

(Ref: Robbins/10th/511)

Takayasu arteritis: Takayasu arteritis is a **granulomatous vasculitis** of **medium** and **larger arteries** characterized principally by ocular disturbances and marked weakening of the pulses in the upper extremities (hence the name ***pulseless disease***).

Takayasu arteritis **classically involves the aortic arch.** In a third of patients, it also affects the remainder of the aorta and its branches, with **pulmonary artery** involvement in half of cases; **coronary** and **renal arteries** may be similarly affected.

Takayasu aortitis shares many attributes with giant cell aortitis, including clinical features and histology; indeed, the distinction is typically made **based on the age** of the patient. Those **over 50 years** of age are designated as **giant cell aortitis,** while those **under 50** are designated as **Takayasu aortitis.**

(Ref: Robbins/10th/512)

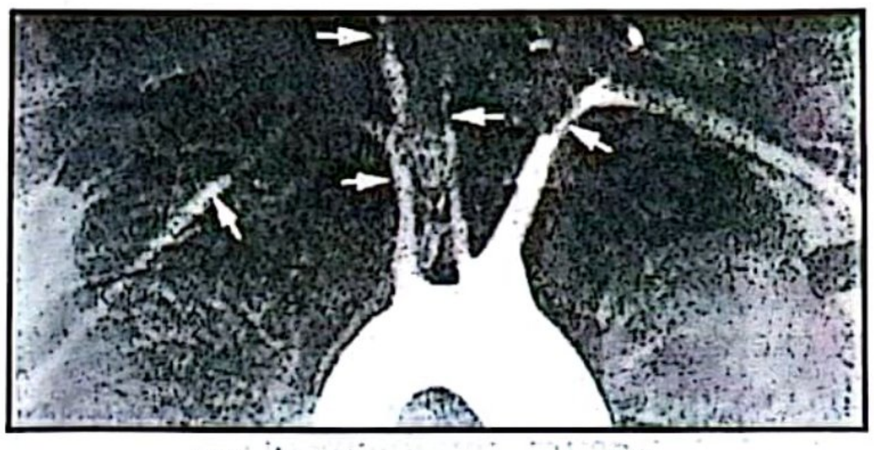


Fig: Takayasu arteritis.

{Aortic arch angiogram showing narrowing of brachiocephalic, carotid, and subclavian arteries *(arrows)*}

Polyarteritis nodosa (PAN): PAN is a **systemic vasculitis** of **small- or medium-sized muscular arteries** that typically affects **renal** and **visceral vessels** but **spares the pulmonary circulation.**

Vessels of the kidneys, heart, liver, and gastrointestinal tract are involved in descending order of frequency.

The **cause** remains **unknown** in the majority of cases. PAN is primarily a disease of **young adults** but can occur in all age groups.

Clinical manifestations result from ischemia and infarction of affected tissues and organs. Typical presentation involves some combination of **rapidly accelerating hypertension** due to renal artery involvement; **abdominal pain** and **bloody stools** caused by vascular gastrointestinal lesions; **diffuse myalgias**; and **peripheral neuritis**, predominantly affecting motor nerves. Renal involvement is often a major cause of mortality. Untreated, PAN is typically fatal; however, immunosuppression can yield remissions or cure in 90% of cases.

(Ref: Robbins/10th/513)

Kawasaki disease: It is an acute, febrile, usually **self-limited illness** of **infancy** and **childhood** associated with **large- to medium-sized vessel arteritis** (80% of the patients are younger than 4 years of age).

In genetically susceptible persons, a variety of **infectious agents** (mostly **viral**) have been posited to trigger the disease.

Its clinical significance stems from the involvement of coronary arteries. Coronary arteritis can result in aneurysms that rupture or thrombose, causing **myocardial infarction**.

(Ref: Robbins/10th/513)

Granulomatosis with polyangiitis (Previously called Wegener granulomatosis): It is a necrotizing vasculitis characterized by the **triad** of-

- **Acute necrotizing granulomas** of the upper respiratory tract (ear, nose, sinuses, throat) or the lower respiratory tract (lung) or both.
- **Necrotizing or granulomatous vasculitis** affecting small to medium-sized vessels (e.g. capillaries, venules, arterioles, and arteries), most prominent in the lungs and upper airways but affecting other sites as well.
- **Focal necrotizing, often crescentic, glomerulonephritis.**

(Ref: Robbins/10th/514)

Churg-strauss syndrome: Churg-Strauss syndrome (also called ***allergic granulomatosis and angiitis***) is a **small-vessel necrotizing vasculitis** classically associated with asthma, allergic rhinitis, lung infiltrates, peripheral eosinophilia, extravascular necrotizing granulomas, and a striking eosinophilic infiltration of vessels and tissues.

Cutaneous involvement (with palpable purpura), **gastrointestinal bleeding**, and **renal disease** (primarily as focal and segmental glomerulosclerosis) are the major associations. Cytotoxicity produced by the myocardial eosinophilic infiltrates often leads to cardiomyopathy; cardiac involvement is seen in 60% of patients and is a major cause of morbidity and death.

(Ref: Robbins/10th/515)

Thromboangiitis obliterans (Buerger disease): Thromboangiitis obliterans is characterized by segmental, thrombosing, acute and chronic inflammation of **medium and small-sized arteries**, especially the **tibial** and **radial** arteries, that often leads to **vascular insufficiency**, typically of the **extremities.**

It occurs almost exclusively in **heavy cigarette smokers**, usually **before the age of 35.**

Clinical features:

- Raynaud phenomenon
- Instep foot pain induced by exercise (instep claudication)
- Superficial nodular phlebitis (venous inflammation)
- Severe pain—even at rest (due to the neural involvement)
- Chronic extremity ulcerations, progressing over time to frank gangrene.

(Ref: Robbins/10th/515)

Raynaud Phenomenon

Raynaud phenomenon: Raynaud phenomenon results from **exaggerated vasoconstriction of arteries and arterioles in responses to cold or emotion**. It most commonly affects the **extremities**, particularly the **fingers and toes**, but also occasionally the **nose, earlobes**, or **lips**.

The involved digits classically show **"red, white, and blue" color changes** from most proximal to most distal, correlating with **proximal vasodilation, central vasoconstriction**, and more **distal cyanosis**.

(Ref: Robbins/10th/516)

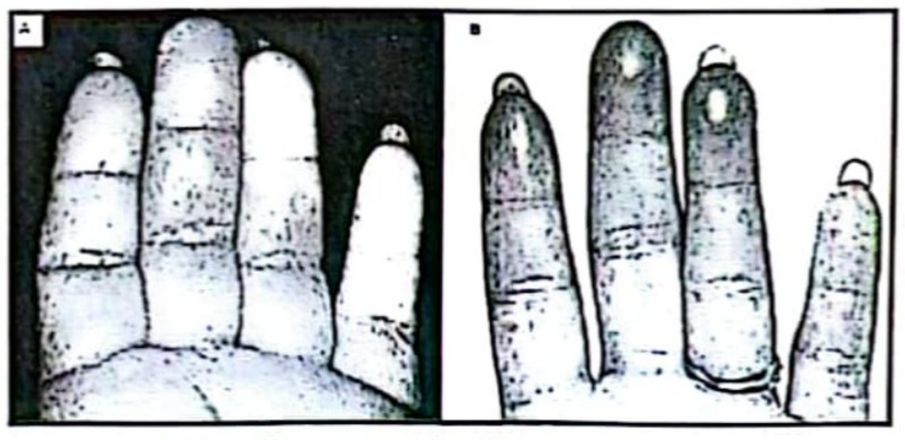


Fig: Raynaud phenomenon.

Types: Raynaud phenomenon can be a primary entity or secondary to other disorders.

1. **Primary Raynaud phenomenon** (previously called Raynaud disease)**:** Caused in response to cold or emotional stresses.
2. **Secondary Raynaud phenomenon:** Caused by other diseases like SLE, scleroderma, Buerger disease, or even atherosclerosis.

(Ref: Robbins/10th/516)

Varicose Veins

(Important for VIVA)

Varicose veins: Varicose veins are **abnormally dilated, tortuous veins** produced by prolonged, increased intraluminal pressure with vessel dilation and incompetence of the venous valves.

The **superficial veins** of the **upper** and **lower leg** are commonly involved because venous pressures in these sites can be markedly elevated (up to 10 times normal) by prolonged dependent posture. Varicosities in two other sites also deserve special mention: **esophageal varices & hemorrhoids.**

(Ref: Robbins/10th/517)

Fig: Varicose veins of the leg (*arrow*).

CHAPTER 02

THE HEART

Diseases of Heart

Q. Name major cardiac diseases. (CMU-22Nv,12Ju)
Q. What are the congenital anomalies of the heart? (CU-20M)
Q. Classify congenital heart disease. (CMU-22M, RU-19Nv,18M)
Q. Enumerate the congenital heart diseases. (CMU-23M, RU-15Ja, CU-11Ja)
Q. Enumerate the ischemic heart diseases. (DU-22Nv,21Ja,20Nv/M,19Nv, RMU-22M, SUST-21Nv)
Q. Name the tumours of heart.

Ans.

Diseases of heart:

A) **Heart failure:**
- Left-sided heart failure
- Right-sided heart failure

B) **Congenital heart disease:** ***(Very Important for VIVA)***

1. **Acyanotic (left-to-right shunts):**
   - Atrial septal defect (ASD)
   - Patent foramen ovale
   - Ventricular septal defect (VSD)
   - Patent ductus arteriosus (PDA)
2. **Cyanotic (right-to-left shunts):**
   - Tetralogy of Fallot
   - Transposition of the great arteries
   - Tricuspid atresia
3. **Obstructive lesions:**
   - Coarctation of the aorta
   - Pulmonary stenosis & atresia
   - Aortic stenosis & atresia

C) Ischaemic heart disease (IHD): *(Very Important for VIVA)*
- Angina pectoris
- Myocardial infarction (MI)
- Chronic ischaemic heart disease

D) Arrhythmias:
- Sudden cardiac death (SCD)

E) Hypertensive heart disease:
- Systemic (left-sided) hypertensive heart disease
- Pulmonary (right-sided) hypertensive heart disease (Cor pulmonale)

F) Valvular heart disease:
- Aortic stenosis (AS)
- Aortic regurgitation (AR)
- Mitral stenosis (MS)
- Mitral regurgitation (MR)
- Rheumatic fever & rheumatic heart disease
- Infective endocarditis (IE)
- Noninfected vegetations
  - Nonbacterial thrombotic endocarditis (NBTE)
  - Endocarditis of Systemic Lupus Erythematosus (Libman-Sacks Disease)
- Carcinoid heart disease
- Complications of prosthetic valves

G) Cardiomyopathies:
- Dilated cardiomyopathy (DCM)
- Arrhythmogenic cardiomyopathy
- Hypertrophic cardiomyopathy
- Restrictive cardiomyopathy
- Myocarditis
- Other causes of myocardial disease
  - Cardiotoxic drugs
  - Radiation

H) Pericardial disease:
1. Pericardial effusion and hemopericardium
2. Pericarditis
   - Acute pericarditis
   - Chronic or healed pericarditis

I) Tumors of the heart:

1. Primary cardiac tumors:
- **Benign:**
  - Myxoma (most common primary tumour of the adult heart)
  - Fibroma
  - Lipoma
  - Papillary fibroelastoma
  - Rhabdomyoma
- **Malignant:**
  - Sarcoma (angiosarcoma).

2. Secondary or metastatic neoplasms (most frequently from lung and breast carcinomas, melanomas, leukemias, and lymphomas).

(Ref: Robbins/10th/527-580)

Nice to Know:

Overview of cardiac pathophysiology: Cardiovascular dysfunction can be attributed to one (or more) of six principal mechanisms:

1. **Failure of the pump** (the so-called systolic and diastolic dysfunction)
2. **Obstruction to flow** (e.g. calcific aortic valve stenosis or systemic hypertension or aortic coarctation)
3. **Regurgitant flow**
4. **Shunted flow**
5. **Disorders of cardiac conduction** (e.g. uncoordinated cardiac impulses or blocked conduction pathways can cause arrhythmias)
6. **Rupture of the heart or a major vessel** (may lead to massive blood loss, hypotensive shock, and death).

(Ref: Robbins/10th/529)

Chest Pain

Q. List the causes of chest pain. (RU-08Ju)

Ans.

Common causes of chest pain:

A. Central:

1. **Anxiety / emotion**
2. **Cardiac**
   - Myocardial ischaemia (angina)
   - Myocardial infarction
   - Myocarditis
   - Pericarditis
   - Mitral valve prolapse syndrome
3. **Aortic**
   - Aortic dissection
   - Aortic aneurism
4. **Oesophageal**
   - Oesophagitis
   - Oesophageal spasm
   - Mallory-weiss syndrome
5. **Pulmonary embolus**
6. **Mediastinal:** Malignancy.

B. Peripheral:

1. **Lungs / pleura**
   - Pulmonary infarct
   - Pneumonia
   - Pneumothorax
   - Malignancy
   - Tuberculosis
   - Connective tissue disorders
2. **Musculoskeletal**
   - Osteoarthritis
   - Rib fracture/injury

- Intercostal muscle injury
- Costochondritis (Tietze's syndrome)
- Intercostal muscle injury

3. **Neurological**
   - Prolapsewd intervertebral disc
   - Herpes zoster
   - Thoracic outlet syndrome.

(Ref: Davidson's/23rd/177)

Congenital Heart Disease

Q. Short note: Congenital heart disease (CHD).

Ans.

Congenital heart disease: Congenital heart disease (CHD) refers to abnormalities of the heart or great vessels that are present at birth.

Most CHD arises from faulty embryogenesis during **gestational weeks 3 to 8**, when major cardiovascular structures form and begin to function.

Incidence: 5% of live births.

Clinical features: Most of the various structural anomalies in CHD can be organized into three major categories according to the major functional abnormalities they cause:

- *Left-to-right shunt*
- *Right-to-left shunt*
- *Obstruction*

{***N.B:*** A **shunt** is an abnormal communication between chambers or blood vessels. Abnormal channels permit blood flow down pressure gradients from the left (systemic) side to the right (pulmonary) side of the circulation or vice versa.}

1. **Right to left shunt (*cyanotic* congenital heart disease): *(Very Important for VIVA)***

   Clinical features:
   - Hypoxemia and **cyanosis** (a dusky blueness of the skin and mucous membranes)
   - Paradoxical embolism
   - Clubbing of the tips of the fingers and toes (hypertrophic osteoarthropathy)
   - Polycythemia
   - Clubbing of the tips of the fingers and toes

   Examples:
   - Tetralogy of Fallot
   - Transposition of the great arteries
   - Persistent truncus arteriosus
   - Tricuspid atresia
   - Total anomalous pulmonary venous connection

2. **Left-to-right shunts (*acyanotic* congenital heart disease): *(Very Important for VIVA)***

   Clinical features:
   - Not initially associated with cyanosis, but may be cyanotic (late cyanotic congenital heart disease, or ***Eisenmenger syndrome***).
   - Right ventricular hypertrophy (RVH)

   Examples:
   - Atrial septal defect (ASD)

- Ventricular septal defect (VSD)
- Patent ductus arteriosus (PDA)

3. **Obstructive congenital heart disease:** Occurs when there is **abnormal narrowing** of chambers, valves, or blood vessels.

Examples:
- Coarctation of the aorta
- Pulmonary stenosis & atresia
- Aortic stenosis & atresia.

(***N.B:*** A complete obstruction is called an **atresia.**)

(Ref: Robbins/10th/534-536)

Q. Short note: Fallot's tetralogy / the tetralogy of Fallot. (RU-17Nv, CU-13Ju)
Ans.

Fallot's tetralogy: The **four cardinal features** of the tetralogy of Fallot (TOF) are- ***(V.V.I for VIVA)***

1) Ventricular septal defect (VSD)
2) Obstruction of the right ventricular outflow tract (subpulmonary stenosis)
3) An aorta that overrides the VSD
4) Right ventricular hypertrophy.

The first three features result embryologically from anterosuperior displacement of the infundibular septum, and the right ventricular hypertrophy is a secondary consequence of the pressure overload.

Clinical features:
1. Even untreated, TOF can be tolerated into adulthood
2. As the child grows, the heart increases in size.
3. Most infants with TOF are cyanotic from birth or soon thereafter (**classic TOF**); some may not show cyanosis (so-called "**pink tetralogy**").

Morphology: The heart is typically enlarged and is classically **"boot-shaped"** due to marked right ventricular hypertrophy.

Treatment: Complete surgical repair is possible for classic TOF but is more complicated for persons with pulmonary atresia and dilated bronchial arteries.

(Ref: Robbins/10th/538)

Heart Failure

Q. What is heart failure?
Ans.
Heart failure: Heart failure is defined as the condition in which a heart cannot pump blood to adequately meet the metabolic demands of peripheral tissues, or can do so only at elevated filling pressures.

(Ref: Robbins/10th/530)

Nice to Know:

Cardiac hypertrophy: Pathophysiology and progression to heart failure: *Sustained increase in mechanical work of either ventricle due to pressure overload, volume overload, or trophic signals (e.g., those mediated through the activation of β-adrenergic receptors) causes myocytes to increase in size (cellular hypertrophy); cumulatively, this increases the size and weight of the heart.*

(Ref: Robbins/10th/530)

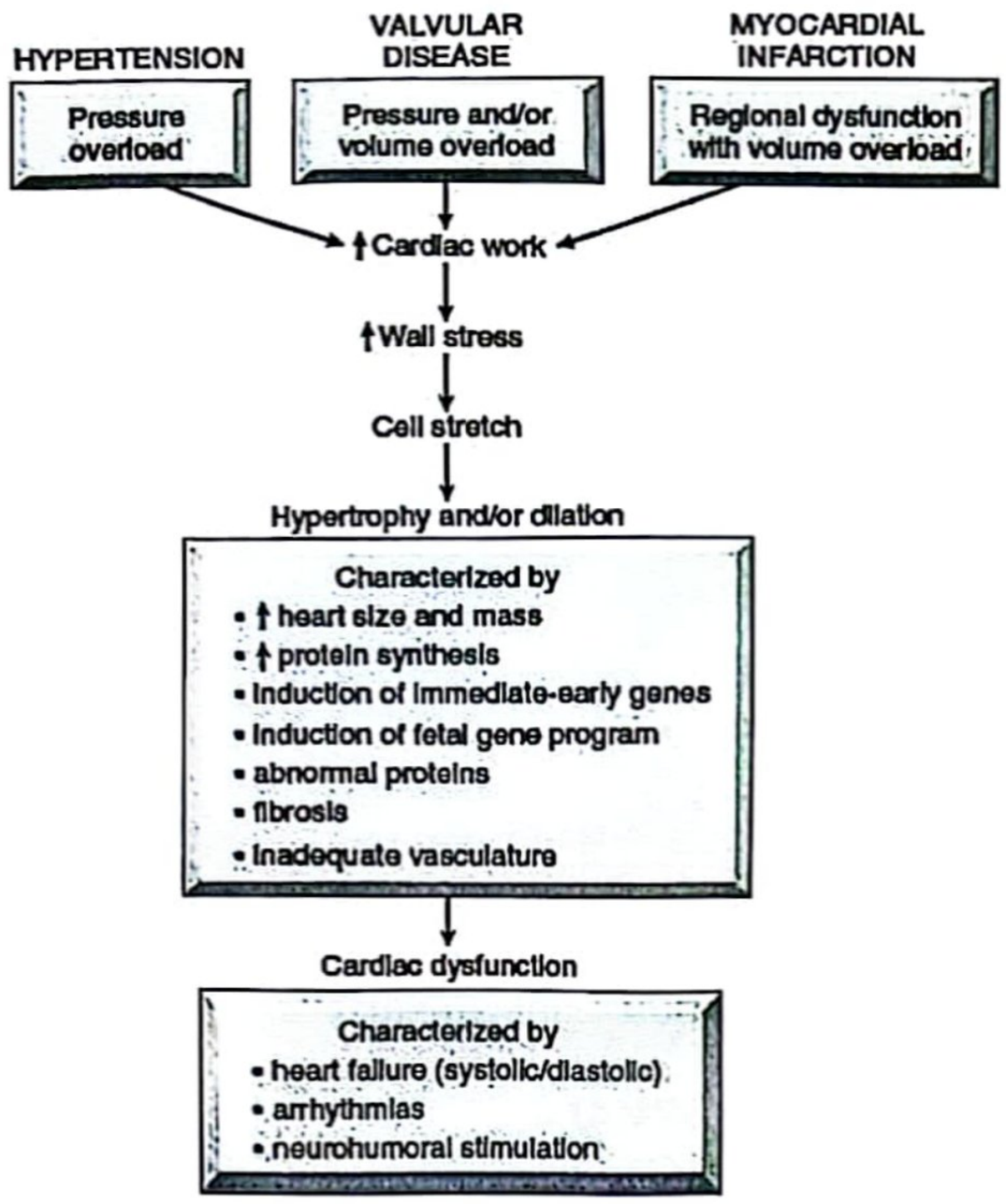


Fig: Schematic representation of the causes and consequences of cardiac hypertrophy.
(Ref: Robbins/10th/532)

Pressure-overload & volume-overload hypertrophy: The pattern of hypertrophy reflects the nature of the stimulus.

- In ***pressure-overload hypertrophy*** (e.g. due to hypertension or aortic stenosis), new sarcomeres are predominantly assembled in parallel to the long axes of cells, expanding the cross-sectional area of myocytes in ventricles and causing a concentric increase in wall thickness.
- In contrast, ***volume-overload hypertrophy*** (e.g. due to valvular regurgitation) is characterized by new sarcomeres being assembled in series within existing sarcomeres, leading primarily to ventricular dilation. As a result, in dilation due to volume overload, or dilation that accompanies failure of a previously pressure overloaded heart, the wall thickness may be increased, normal, or less than normal. Consequently, heart weight, rather than wall thickness, is the best measure of hypertrophy in dilated hearts.

(Ref: Robbins/10th/530)

Q. What are the causes of left-sided heart failure?
Q. What are the morphologic changes that occur in various organs in left heart failure?
Ans.

Causes of left-sided heart failure: Left-sided heart failure is most often caused by the following:

1. Ischemic heart disease (IHD)
2. Hypertension
3. Aortic and mitral valvular disease
4. Primary myocardial diseases.

Morphologic changes that occur in various organs in left heart failure:

1. **Heart:**
   - Hypertrophied and dilated left ventricle
   - Secondary enlargement of the left atrium
   - Thrombus formation
   - Myocardial infarction & valvular deformity
2. **Lung:**
   - Pulmonary congestion and **edema**, with heavy, wet lungs
   - Hemosiderin-laden macrophages in the alveoli (also known as **siderophages,** or ***heart failure cells***)
   - Pleural effusion (typically serous)
3. **Kidney:**
   - Reduction in renal perfusion
   - Prerenal azotemia
4. **Brain:**
   - Hypoxic encephalopathy.

(Ref: Robbins/10th/532)

Q. What are the causes of right-sided heart failure?
Q. What are the morphologic changes that occur in various organs in right heart failure?
Ans.

Causes of right-sided heart failure: ***(For VIVA)***

1. Secondary to left-sided heart failure
2. Isolated right-sided heart failure (often referred to as **cor pulmonale**).

Morphologic changes that occur in various organs in right heart failure: ***(For VIVA)***

1. **Heart:**
   - Hypertrophy and dilation of the right atrium and ventricle
   - Rarely- structural defects such as valvular abnormalities or endocardial fibrosis
2. **Liver and portal system:**
   - The liver is usually increased in size and weight (**congestive hepatomegaly**) due to prominent **passive congestion**.
   - Congestion is most prominent around central veins which is reflected as congested red-brown pericentral zones, with relatively normal-colored tan periportal regions, producing the characteristic **"nutmeg liver"** appearance
   - With long-standing severe cases, the central areas can become fibrotic, eventually culminating in **cardiac cirrhosis**
   - Portal venous hypertension also causes enlargement of the spleen with platelet sequestration **(congestive splenomegaly),** and can also contribute to chronic congestion and edema of the bowel wall.
3. **Pleural, pericardial, and peritoneal spaces:** Systemic venous congestion can lead to fluid accumulation **(effusions)** in the pleural, pericardial, or peritoneal spaces (a peritoneal effusion is also called **ascites**).
4. **Subcutaneous tissues:**
   - Edema of the peripheral and dependent portions of the body, especially **foot/ankle (pedal)** and **pretibial edema**, is a **hallmark** of right-sided heart failure.
   - In chronically bedridden patients, **presacral edema** may predominate.
   - Generalized massive edema **(anasarca)** can also occur.

(Ref: Robbins/10th/533)

Important Clinical Correlation for VIVA

Q. What are the cardinal features of left ventricular failure?
Ans.
- Pulsus alternans
- Gallop rhythm
- Bilateral basal crepitations.

Q. What are the cardinal features of right ventricular failure?
Ans.
- Raised JVP
- Tender hepatomegaly
- Dependent edema.

Q. What are the cardinal features of congestive cardiac failure?
Ans.
- Bilateral basal crepitations
- Raised JVP
- Tender hepatomegaly
- Dependent edema.

Ischaemic Heart Disease (IHD)

(V.V.I. for VIVA)

Q. What do you mean by ischaemic heart disease? (SU-20M,06Ja, RU-17Nv,09Ju, CU-05Ja)
Q. Name the ischaemic heart diseases. (DU-22Nv,21Ja,20Nv/M,19Nv,12Ja, RMU-22/21/19M,17Nv/Ja,16Ja,12/11/10Ju, SUST-22Nv/M,21Nv,19M)
Q. Define and classify ischaemic heart disease (IHD). (RU-20M,14Ja, SU-19Nv)
Q. Classify various types of ischaemic heart disease. (SU-20M, CU-19M)
Q. Mention the conditions of IHD. (SU-06Ja,05M/Ja)
Ans.
Ischemic heart disease (IHD): It represents a group of related entities resulting from **myocardial ischemia—an imbalance between myocardial supply (perfusion) and cardiac demand** for oxygenated blood.
(Ref: Robbins/10th/542)

Types / syndromes of IHD: IHD can declare itself through one or more of the following clinical presentations:

1. Angina pectoris (literally "chest pain") - in which ischemia is not severe enough to cause infarction
   - Stable (typical) angina (*pain precipitated by **exertion***)
   - Unstable or crescendo angina (*prolonged or recurrent pain **at rest***)
   - Prinzmetal angina (*intermittent chest pain **at rest** caused by **vasospasm***)
2. Myocardial infarction (MI) - in which ischemia causes frank cardiac necrosis
3. Chronic IHD with heart failure
4. Sudden cardiac death (SCD).

(Ref: Robbins/10th/542,543; BRS Pathology/5th/137)

Q. Why IHD is often called coronary artery disease? *(Important for VIVA)*
Ans.

IHD is often called coronary artery disease: In more than 90% of cases, **myocardial ischemia** results from **reduced blood flow** due to **obstructive atherosclerotic lesions** in the **epicardial coronary arteries**; consequently, IHD is frequently referred to as **coronary artery disease (CAD).**

(Ref: Robbins/10th/542)

*(**N.B: In most cases there is a long period (up to decades) of **silent**, slow progression of coronary lesions before the sudden onset of symptoms. Thus, IHD is often the **late manifestation** of coronary atherosclerosis that began during childhood or adolescence.)*

(Ref: Robbins/9th/538)

Nice to Know:

Atherosclerotic lesions in coronary arteries are distributed in one or more of the three major coronary arterial trunks, the highest incidence being in the **anterior descending branch of the left coronary (LAD)**, followed in decreasing frequency, by the **right coronary artery (RCA)** and still less in **circumflex branch of the left coronary (CXA)**. About one-third of cases have ***single-vessel disease,*** most often left anterior descending arterial involvement; another one-third have ***two-vessel disease,*** and the remainder has ***three major vessel disease.***

(Ref: Harsh Mohan/7th/407)

Q. What are the risk factors of ischemic heart disease (IHD)? (DU-13Ja, SU-19Nv,10Ja, RU-12Ja,09Ju, CU-11Ja)
Q. Mention the risk factors of myocardial infarction. (RMU-22Nv, BUP-22Nv, SU-15Ja)
Q. Mention the major risk factors of myocardial infarction. (DU-12Ja)
Q. Short note: Risk factors of MI. (RU-08Ja)
Ans.

Risk factors for IHD / MI: *(Very Important for VIVA)*

Major risk factors:

Non-modifiable (constitutional):

1. Genetic abnormalities
2. Family history
3. Increasing age
4. Male gender

Modifiable (potentially controllable):

1. Hyperlipidaemia (more specifically hypercholesterolemia)
2. Hypertension
3. Cigarette smoking
4. Diabetes

Additional risk factors:

1. Inflammation & evevated C-reactive protein (CRP)
2. Hyperhomocystinemia
3. Metabolic syndrome
4. Lipoprotein a [Lp(a)]
5. Factors affecting hemostasis (Prothrombotic factors and elevated fibrinogen levels)
6. Other factors
   - Obesity
   - Lack of exercise / physical inactivity
   - High carbohydrate intake
   - Competitive, stressful lifestyle (type A personality).

(Ref: Robbins/10th/494; BRS Pathology/5th/124; Harsh Mohan/7th/373)

Q. Discuss the pathogenesis of IHD. (RU-17Nv)

Ans.

Pathogenesis of IHD: The dominant cause of the IHD is ***partial or complete interruption of arterial blood flow*** to the myocardium resulting **insufficient coronary perfusion relative to myocardial demand.**

It is convenient to consider the etiology of IHD under three broad headings:

i) **Coronary atherosclerosis:** Chronic, progressive ***atherosclerotic narrowing*** of the epicardial coronary arteries.

ii) **Variable degrees of superimposed acute plaque change:** Rupture, superficial erosion, ulceration, fissuring, or deep haemorrhage etc.

iii) **Non-atherosclerotic causes:**
- Vasospasm
- Stenosis of coronary ostia
- Coronary arteries
- Thrombotic diseases (e.g. polycythaemia vera, sickle cell anaemia)
- Embolism
- Trauma to coronary arteries
- Aneurysms
- Compression of a coronary from outside.

(Ref: Robbins/10th/542; BRS Pathology/5th/137; Harsh Mohan/7th/408)

Q. Mention the consequences of myocardial ischemia. (For VIVA)

Ans.

Consequences of myocardial ischemia (IHD): Depending upon the suddenness of onset, duration, degree, location and extent of the area affected by myocardial ischaemia, the consequences may be:

- Stable angina
- Unstable angina
- Myocardial infarction (MI)
- Sudden cardiac death.

(Ref: Robbins/10th/543; Harsh Mohan/7th/408)

Q. What is acute coronary syndrome? *(Important for VIVA)*

Ans.

Acute coronary syndrome: The **triad** of unstable angina, acute myocardial infarction (MI), and sudden cardiac death are sometimes referred to as ***acute coronary syndrome***.

(Ref: Robbins/10th/543; Harsh Mohan/7th/408)

Angina Pectoris

(Important for VIVA)

Q. Define angina pectoris. What are the types of it?

Q. Short note: Angina pectoris. (DU-21Oct/M, RU-19M, CU-18Nv)

Ans.

Angina pectoris: Angina pectoris (literally **"chest pain")** is characterized by paroxysmal and usually recurrent attacks of **substernal** or **precordial chest discomfort** caused by ***transient*** (15 seconds to 15 minutes) ***myocardial ischemia*** that is ***insufficient to induce myocyte necrosis***.

(Ref: Robbins/10th/543)

Or,

Angina pectoris is the **episodic chest pain** caused by **inadequate oxygenation of the myocardium.**

(Ref: BRS Pathology/5th/137)

Types of angina:

1. **Stable (typical) angina:** It is the **most common** form of angina. It is classically described as a **crushing** or **squeezing substernal sensation** that can radiate down the **left arm** or to the **left jaw** ***(referred pain)***. The **pain** is **precipitated by exertion** (i.e. physical activity, emotional excitement or psychological stress) and is **relieved by rest (decreasing demand)** or administering **vasodilators**, such as nitroglycerin and calcium channel blockers (thereby **increasing perfusion).**

   It is caused by an **imbalance in coronary perfusion** (due to chronic stenosing coronary atherosclerosis) **relative to myocardial demand.**

2. **Unstable or crescendo angina:** It is a pattern of increasingly frequent, **prolonged (>20 min),** or severe angina, **precipitated by** progressively **lower levels of physical activity** or **even occurring at rest.**

   It is generally caused by disruption of an atherosclerotic plaque with superimposed thrombosis. It can also be caused by distal embolization of the thrombus, and/or vasospasm.

   Unstable angina serves as a **warning for MI,** that's why it is referred to as **'pre-infarction angina'** or **'acute coronary insufficiency'.**

3. **Prinzmetal variant angina:** It is an uncommon form of **episodic myocardial ischemia** caused by **coronary artery spasm.**

(Ref: Robbins/10th/543; BRS Pathology/5th/137; Harsh Mohan/7th/409)

(N.B: Myocardial infarction differs from unstable angina, since there is evidence of myocardial necrosis.)
(Ref: Davidson's/23rd/493)

N.B: In angina, there is no elevation of enzymes in the blood as there is no irreversible myocardial injury.)
(Ref: Harsh Mohan/7th/409)

Myocardial Infarction (MI)

Q. What is myocardial infarction (MI)? What are the types of MI?
Ans.
Myocardial infarction (MI): MI, also commonly referred to as **"heart attack,"** is the **death of cardiac muscle** due to **prolonged ischemia.**

It is the most important and feared consequence of coronary artery disease.
(Ref: Robbins/10th/543; Harsh Mohan/7th/409)

Patterns of MI: There are two distinct patterns of myocardial ischemic necrosis:

1. **Transmural (ful thickness) infarction:** Ischemic necrosis involves the **full or nearly full thickness of the ventricular wall** (from the ***endocardium to the epicardium***) in the distribution of the affected coronary artery.

2. **Subendocardial (non-transmural) infarction:** Ischemic necrosis involves the **inner third of the ventricular wall.** It occurs as a result of a plaque disruption followed by a coronary thrombus that becomes lysed (therapeutically or spontaneously) before myocardial necrosis extends across the full thickness of the wall.

(Ref: Robbins/10th/546; BRS Pathology/5th/138; Harsh Mohan/7th/410)

Multifocal microinfarction is another pattern of myocardial ischemic necrosis which is seen when there is pathology involving only **smaller intramural vessels.**

(Ref: Robbins/10th/547)

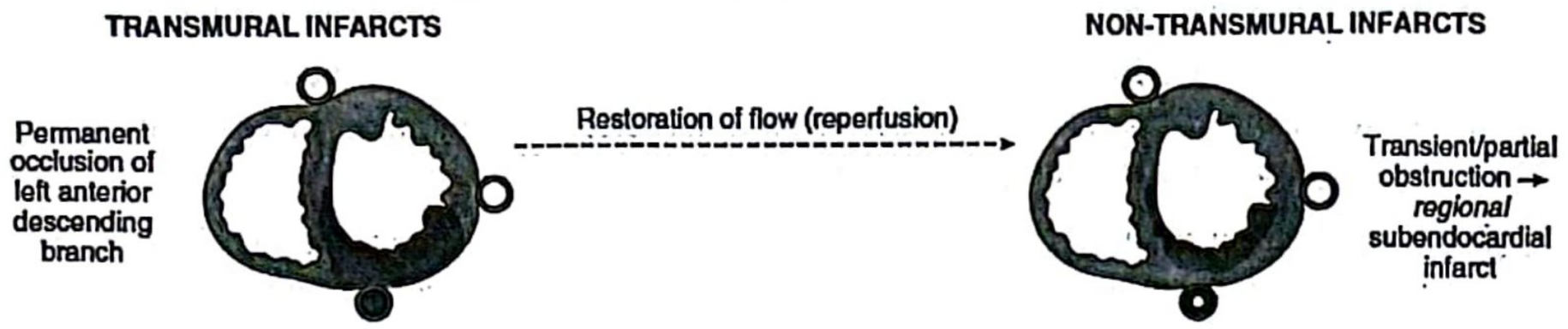

TRANSMURAL INFARCTS
NON-TRANSMURAL INFARCTS
Permanent occlusion of left anterior descending branch
Restoration of flow (reperfusion)
Transient/partial obstruction → regional subendocardial infarct

Fig: Transmural and non-transmural infarction.

Nice to Know:

Owing to the characteristic **ECG changes** resulting from myocardial ischemia or necrosis in various distributions, a **transmural infarct** is sometimes referred to as an **"ST elevated MI" (STEMI)** and a **subendocardial infarct** as a **"non–ST elevated MI" (NSTEMI).**

(Ref: Robbins/10th/550)

Nice to Know:

Infarcts are **most frequently** located in the **left ventricle.** ***Right ventricle is less susceptible to infarction*** due to its **thin wall,** having **less metabolic requirements** and is thus **adequately nourished** by the **thebesian vessels.**

Left atrium is relatively protected from infarction because it is supplied by the oxygenated blood in the left atrial chamber.

(Ref: Harsh Mohan/7th/410)

Q. Discuss in brief the epidemiology of MI. (RU-08Ju)

Ans.

Incidence and risk factors / epidemiology of MI:

- Myocardial infarction is the most important cause of morbidity from IHD and is one of the leading causes of death in the Western world.
- Roughly 1.5 million individuals in the United States suffer an MI each year.
- It can occur at virtually any age, but the frequency rises progressively with increasing age. Nearly 10% occur in people under age 40, and 45% occur in people under age 65.
- Blacks & whites are equally affected.
- Men are at significantly greater risk of MI than women.

(Ref: Robbins/10th/543; BRS Pathology/5th/137)

Q. Discuss in brief about the pathogenesis of MI (myocardial infarction). (DU-21Ja,20Nv/M, 19Nv, CMU-22Nv, RMU-21M,08Ju, SU-15Ja)

Ans.

Pathogenesis of MI:

A) Coronary arterial occlusion:

a) Thrombotic occlusion of coronary artery: The following sequence of events likely underlies most MIs-

- An atheromatous plaque is eroded or suddenly disrupted by endothelial injury, intraplaque hemorrhage, or mechanical forces, exposing subendothelial collagen and necrotic plaque contents to the blood.
- Platelets adhere, aggregate, and are activated, releasing thromboxane A_2, adenosine diphosphate (ADP), and serotonin—causing further platelet aggregation and vasospasm.
- Activation of coagulation by tissue factor and other mechanisms adds to the growing thrombus.

- Within minutes, the thrombus can evolve to completely occlude the coronary artery lumen.

b) **Non-thrombotic occlusion of coronary artery:** The mechanisms include-

1. **Vasospasm** with or without coronary atherosclerosis, perhaps in association with platelet aggregation or due to drug ingestion (e.g. cocaine or ephedrine).
2. **Emboli** from the left atrium in association with atrial fibrillation, a left-sided mural thrombus, vegetations of infective endocarditis, intracardiac prosthetic material; or paradoxical emboli from the right side of the heart or the peripheral veins, traversing a patent foramen ovale and into the coronary arteries.
3. **Uncommon causes** of MI without atherothrombosis include disorders of small intramural coronary vessels (e.g. vasculitis), hematologic abnormalities (e.g. sickle cell disease), amyloid deposition in vascular walls, vascular dissection, marked hypertrophy (e.g. due to aortic stenosis), lowered systemic blood pressure (e.g. shock), or inadequate myocardial "protection" during cardiac surgery.

B) **Myocardial response:** Coronary arterial obstruction diminishes blood flow to a region of myocardium, causing ischemia, rapid myocardial dysfunction, and eventually—with prolonged vascular compromise—**myocyte death**. The anatomic region supplied by that artery is referred to as the **area at risk**. The outcome depends predominantly on the severity and duration of flow deprivation.

(Ref: Robbins/10th/544)

(***N.B***: Myocardial ischemia leads to loss of function within 1 to 2 minutes but causes necrosis only after 20 to 30 minutes.)

(Ref: Robbins/10th/553)

Q. Give the morphology of MI. (DU-03M/Ja, RU-04M) ***(Very Important for VIVA)***
Q. Write the morphological changes in MI. (DU-10Ja, CU-12Ju)
Q. Discuss the light microscopic changes occur in myocardium after MI. (SU-10Ja)
Ans.

Morphology of MI: The gross and microscopic appearance of an infarct depends on the interval of time between the MI and death.

Time	Gross features	Light microscopic features
Reversible injury		
0 – ½ hour	None	None
Irreversible injury		
½ - 4 hours	None	Usually none; variable waviness of fibers at border
4 - 12 hours	Dark mottling (occasional)	Early **coagulative necrosis**; edema; hemorrhage
12 - 24 hours	Dark mottling	Ongoing **coagulation necrosis**; pyknosis of nuclei; myocyte hypereosinophilia, marginal contraction band necrosis, early neutrophilic infiltrate
1 - 3 days	Mottling with yellow-tan infarct center	Coagulation necrosis, with loss of nuclei & striations; interstitial **infiltrate of neutrophils**
3 - 7 days	Hyperemic border; central yellow-tan softening	Beginning disintegration of dead myofibers, with dying neutrophils; early phagocytosis of dead cells by **macrophages** at infarct border
7 - 10 days	Maximally yellow-tan & soft, with depressed & red-tan margins	Well-developed **phagocytosis** of dead cells; **granulation tissue** at margins
10 - 14 days	Red-gray depressed infarct borders	Well-established **granulation tissue** with new blood vessels and collagen deposition

2 - 8 weeks	Gray-white scar, progressive from border toward core of infarct	Increased collagen deposition, with decreased cellularity
> 2 months	Scarring complete	Dense collagenous scar

(Ref: Robbins/10th/547)

Q. What types of necrosis occurs in myocardial infarction? (*Very Important for VIVA*)

Ans.

Necrosis in myocardial infarction: Coagulative necrosis.

(Ref: BRS Pathology/5th/137)

Q. Mention the clinical features of myocardial infarction (MI). *(Very Important for VIVA)*

Ans.

Clinical features of myocardial infarction (MI):

- Prolonged (more than 30 minutes) **central chest pain** described as ***crushing***, ***stabbing***, or ***squeezing***
- Anxiety and fear of impending death
- Nausea and vomiting
- Hypotension
- Rapid, weak pulse
- Profuse sweating (diaphoresis)
- Breathlessness
- Collapse/syncope
- **Painless** or **'silent' MI** (asymptomatic): ***Older patients*** or those with ***diabetes mellitus***.

(Ref: Robbins/10th/550; Davidson's/23rd/495)

Nice to Know:

Painless or 'silent' MI: In as many as 25% of patients the onset of MI is entirely **asymptomatic** (e.g. in the setting of ***diabetic neuropathy***), and the disease is **discovered** only by **electrocardiographic changes** or **laboratory tests** that show evidence of myocardial damage.

(Ref: Robbins/10th/550)

Q. Mention the biochemical changes in MI. *(Very Important for VIVA)*

Ans.

Biochemical changes in MI:

1. Cessation of aerobic glycolysis within seconds *(due to myocardial ischemia)*.
2. Inadequate production of high-energy phosphate (e.g. Creatine phosphate and ATP) due to onset of anerobic glycolysis.
3. Accumulation of potentially noxious breakdown metabolites (such as lactic acid).
4. Induction of enzymatic change, such as-
   - CK-MB → Rises within 4-6 hours after MI
   - AST → Rises in 12 hours after MI
   - LDH → Rises in 12 hours after MI
5. Release of myoglobin, troponin-I and troponin-T by the injured cardiac myocytes.

(Ref: Robbins/10th/550; Davidson's/22nd/590)

Q. Write the laboratory diagnosis of acute MI. (CU-05Ja, SU-14Ju,06Ja,05M/Ja)
Q. Mention the important cardiac markers of myocardial infarction (MI). (DU-22Nv)
Q. Name the different cardiac enzymes related to diagnosis of MI. (DU-21Ja,20Nv/M)
Q. Name the enzymes of cardiac importance with clinical significance. (CU-08Ja)
Q. Mention the enzymatic changes that occur in MI. (RU-12Ja)
Q. Mention 3 important biochemical markers of myocardial infarction with change of time. (DU-08Ja)
Q. Name 4 biochemical indicators of myocardial infarction (MI). (DU-07Ja)

Q. Write the biochemical markers of myocardial infarction with their time of onset, peak and fall. (SMU-23M)
Q. What are the enzymes you will estimate for early/recent myocardial infarction? (RU-10Ju)
Q. Mention the enzymes with their interpretation used in myocardial infarction (MI). (SU-20M)
Q. Short note: Cardiac enzymes and protein. (DU-14Ju)
Q. Short note: Cardiac enzymes of clinical significance. (DU-19M)
Q. Short note: Cardiac enzymes. (CU-14Ju)

Ans. ***(Very Important for VIVA)***

Diagnosis of acute MI: MI is diagnosed by **history, clinical symptoms, laboratory tests** for the presence of **myocardial enzymes** and **proteins** in the plasma, and characteristic **ECG changes.**

1. **History**
2. **Clinical symptoms** (*see above*)
3. **Laboratory diagnosis:**
   - i) **ECG changes**
     - ST segment elevation (or new bundle branch block)
     - Pathological Q-wave formation
     - T-wave inversion.
   - ii) **Routine blood examination:** Neutrophilic leukocytosis, raised ESR & C-reactive protein (CRP).
   - iii) **Estimation of cardiac enzymes and proteins (*cardiac biomerkers*):**

Enzymes	Normal value	Enzymatic changes in MI		
		(Time of onset) Rise within	Peaks at	Returns to normal in
CK-MB	**Male:** 55-170 IU/L **Female:** 30-135 IU/L	4-6 hours	12-24 hours	48-72 hours
Troponin-I & Troponin-T	Normally absent	4-6 hours	24-48 hours	5-14 days
AST	10-45 IU/L	12 hours	48 hours	3-4 days
LDH	208-460 IU/L	12 hours	2-3 days	1-2 weeks
Myoglobin			6 hours	48 hours

   - iv) **Chest X-ray** (to demonstrate pulmonary oedema).
   - v) **Echocardiography** (to assess ventricular function and to detect important complications).
   - vi) **Coronary angiography** (for moderate to high risk patients with a view to PCI or urgent CABG).

(Ref: Robbins/10th/550; Davidson's/23rd/497,498; BRS Pathology/5th/138)

*(**Note: Troponin-I** and **CK–MB** elevations are **highly characteristic of myocardial infarction. Total LDH** and **total CK** are **nonspecific indicators** that are passing into disuse in the diagnosis of myocardial infarction. **Myoglobin** is the **most sensitive** of the cardiac markers and is the **earliest to appear** after myocardial infarction; however, it is **not very cardiospecific.**)*

(Ref: BRS Pathology/5th/138)

Nice to Know:

- The **preferred biomarkers** for **myocardial damage** are ***cardiac-specific proteins*** particularly **Troponin-I & Troponin-T** (***the most sensitive and specific biomarkers of MI***). These markers have **nearly complete tissue** ***specificity*** and **high** ***sensitivity***. These are the proteins that regulate calcium-mediated contraction of cardiac and skeletal muscle.
- **C-reactive protein (CRP)** is an ***acute phase reactant*** synthesized primarily by the **liver.** It strongly and independently predicts the risk of MI, stroke, peripheral arterial disease, and sudden cardiac death, even among apparently healthy individuals. Using highly sensitive methods, serum CRP levels of **more than 3 mg/L** are associated with the ***highest risk*** of **cardiovascular disease,** while levels of **1 to 3 mg/L** are associated with ***moderate risk.***

Normal value: <5 mg/L.

(Ref: Robbins/10th/550; Davidson's/23rd/497 + 21st/1296)

Exclusive Questions for VIVA

Q. What is the source of enzymes (cardiac enzymes in plasma) in MI?
Ans.
Myocardial infarction (MI) is the death of cardiac muscle due to prolonged severe ischemia (irreversible cell injury).
Hallmark of irreversible cell injury is membrane leak. So, cardiac enzymes will leak.

Q. What is the most sensititve and specific cardiac marker in MI?
Ans.
Troponin-I is the **most sensitive** and **specific** cardiac marker.

Q. Which cardiac marker is useful for detecting reinfarction in MI?
Ans.
CK-MB is useful for detecting ***reinfarction***, because is returns to its normal level by only 72 hours of infacrtion.

Q. Which is the earliest cardiac marker detected in MI?
Ans.
Myoglobin is the **earliest cardiac marker** to appear after myocardial infarction.

(Ref: Robbins/10th/550; Davidson's/23rd/497; Pathoma Lecture Notes)

Q. Mention the treatment of myocardial infarction (MI).
Q. Mention the therapeutic interventions of MI with their rationale.
Ans.
Therapeutic interventions / treatment of MI:

- **Urgent hospitalization,** preferably in dedicated cardiac unit (CCU)
- **Oxygen supplementation** to improve blood oxygen saturation
- **Morphine** (to relieve pain and improve dyspneic symptoms)
- **Nitrates** (to induce vasodilation and reverse vasospasm)
- **Antiplatelet agents** (such as aspirin, ADP receptor inhibitors, and GPIIb/IIIa inhibitors)
- **Anticoagulant therapy** with unfractionated heparin, low-molecular-weight heparin, direct thrombin inhibitors, and/or factor Xa inhibitors to prevent coronary artery thrombus propagation
- **Beta blockers** (to decrease myocardial oxygen demand and to reduce risk of arrhythmias, unless contraindicated such as in heart failure)
- **Prompt reperfusion** to salvage myocardium, by either fibrinolytic medications or transcatheter interventions
- **Improve myocardial oxygen supply versus demand** by management of other factors, such as anxiety, ischemic pain, abnormal hemodynamics, anemia, and respiratory disorders
- **Early arrhythmia monitoring** and management.

(Ref: Robbins/10th/550; Davidson's/23rd/498)

Q. What are the complications of acute myocardial infarction (MI)? (DU-12Ja,09Ju, RU-17Nv/Ja,16/15Ja,10/09/08/07Ju)
Q. What are the consequences and complications of myocardial infarction? (DU-22Nv,13Ja)

Q. Enumerate the complications of myocardial infarction (MI). (DU-19Nv, BUP-22Nv, RMU-22/21/19/18Nv, SU-20M)

Q. Short note: Complications of MI. (DU-14Ja) ***(Important for VIVA)***

Ans.

Complications of MI: Nearly three-fourths of patients experience one or more of the following complications after an acute MI:

1. **Contractile dysfunction:**
   - Left ventricular failure with hypotension
   - Pulmonary edema
   - Respiratory impairment
   - Severe "pump failure" (cardiogenic shock)
2. **Papillary muscle dysfunction** leading to postinfarct mitral regurgitation.
3. **Right ventricular infarction** leading to right-sided heart failure.
4. **Myocardial rupture:** Rupture complicates only **1% to 5% of MIs**, but is frequently **fatal** when it occurs. It occurs most commonly within **3 to 7 days after infarction**.
   - **Left ventricular free wall rupture** (most common) - usually resulting in rapidly fatal hemopericardium and cardiac tamponade.
   - **Ventricular septal rupture** - creates a VSD with left-to-right shunting.
   - **Papillary muscle rupture** - leads to severe mitral regurgitation.
5. **Arrhythmias:** It is the most common cause of ***sudden death*** in the ***first hour*** following MI. MI-associated arrhythmias include-
   - Heart block of variable degree (including asystole)
   - Bradycardia
   - Supraventricular tachyarrhythmias
   - Ventricular premature contractions or ventricular tachycardia,
   - Ventricular fibrillation.
6. **Pericarditis:** Pericarditis typically appears 2 to 3 days after infarction and then gradually resolves over the next few days. Rarely patients can develop an intense pericarditis weeks after MI *(Dressler syndrome)*.
7. **Chamber dilation:** Because of the weakening of necrotic muscle, there may be disproportionate stretching, thinning, and dilation of the infarcted region (especially with anteroseptal infarcts).
8. **Mural thrombosis**, potentially leading to left-sided thromboembolism.
9. **Ventricular aneurysm**
10. **Progressive heart failure** (chronic IHD).

(Ref: Robbins/10th/551; BRS Pathology/5th/138,139)

(N.B: **One-third** of patients who are unfortunate enough to suffer a **STEMI** at home will **die**, usually of an **arrhythmia** within **1 hour of symptom** onset and **before they can receive medical attention**.)

(Ref: Robbins/10th/551)

Q. Short note: Myocardial infarction. (CU-14Ju)

Ans.

Myocardial infarction: *Please write from above.*

Q. A male of 50 years presented with sudden severe chest pain and sweating. He lost his consciousness for a while and was rushed to the hospital. What is the likely diagnosis? Give the expected biochemical findings in his blood. (DU-17Nv)

Q. A smoker male of 60 years develops sudden excruciating chest pain with sweating of forehead. What is the probable diagnosis? What are the biochemical indicators that will favor the diagnosis? (DU-12Ja)

Q. A male smoker of 55 years develops sudden excruciating chest pain with sweating. What will be the probable diagnosis? What are the biochemical indicators that will favor the diagnosis? (RU-14Ju)

Ans.

Probable diagnosis: Myocardial infarction (MI).

Biochemical indicators:

- CK-MB → Rises within 4 - 6 hours after MI
- Troponin-I & Troponin-T → Rises within 4 - 6 hours after MI.
- AST → Rises within 12 hours after MI
- LDH → Rises within 12 hours after MI.

Q. A 35 years old male presented with severe chest pain. His ECG shows definite ischaemic change. What will be the effect of myocardium? State its complication. (DU-09Ju)

Ans.

Effect on myocardium: Myocardial infarction (coagulation necrosis).

*{**Note:** As there is a severe chest pain and there is definite ischemic change in ECG, this is myocardial infarction, not angina}*

Complications of MI: *Please see above.*

Q. A male of 55 years was brought to the hospital with central chest pain and forehead sweating followed by unconsciousness. What is the probable diagnosis? What are the important investigations to confirm the diagnosis? (DU-21Oct/M)

Q. A man of 50 years was brought to the hospital with the complaint of severe central chest pain and sweating followed by transient unconsciousness. What is the likely diagnosis? Name the laboratory investigations to confirm the diagnosis? (DU-19M)

Q. A diabetic patient of 55 years complaining severe chest pain, sweating and has become unconscious within 1 hour. What is the likely diagnosis? What investigations will you do and what are the expected findings? (DU-11Ju

Ans.

Probable diagnosis: Acute myocardial infarction (MI).

Laboratory investigations: *Please see above.*

Sudden Cardiac Death

Q. Short note: Sudden cardiac death.

Ans.

Sudden cardiac death: Sudden cardiac death (SCD) is defined as **unexpected death from cardiac causes,** either **without symptoms,** or **within 1 to 24 hours of symptom onset.**

(Ref: Robbins/10th/551)

Or,

Sudden cardiac death (SCD) is defined as **unexpected death due to cardiac disease** with **no symptom** or **death <1 hr after symptom** arise.

(Ref: Pathoma Lecture Notes)

The mechanism of SCD is most often a **lethal arrhythmia** (e.g. asystole or ventricular fibrillation).

(Ref: Robbins/10th/551)

Causes of sudden cardiac death (SCD): Ventricular arrhythmia due to-

1. **Coronary artery disease / severe atherosclerosis** (80% to 90% of cases)
2. **Non-atherosclerotic causes** (younger victims):
   - Cardiac conduction abnormalities, hereditary or acquired
   - Dilated or hypertrophic cardiomyopathy
   - Congenital coronary arterial abnormalities
   - Myocarditis
   - Mitral valve prolapse
   - Pulmonary hypertension
   - Other miscellaneous causes, such as pericardial tamponade, pulmonary embolism, systemic metabolic and hemodynamic alterations, catecholamines, and drugs of abuse, particularly cocaine and methamphetamine.

(Ref: Robbins/10th/555)

Vegetative Heart Disease

Q. Name the vegetative heart disease. (RMU-23M)
Q. Enumerate the causes of vegetations in the heart valve. (SU-11/10/09/08Ju,07Ja)
Q. How can you differentiate different vegetations in heart valves? (SU-11/10/09/08Ju)
Q. Differentiate among vegetations of different types of endocarditis. (SU-13Ju)
Q. Enumerate the vegetations in heart. (RMU-22M,14Ja)
Ans.

Vegetative heart diseases: ***(Important for VIVA)***

1. Rheumatic fever & rheumatic heart disease
2. Infective endocarditis (IE)
3. Non-infected (sterile) vegetations
   - Non-bacterial thrombotic endocarditis (NBTE)
   - Endocarditis of systemic lupus erythematosus (Libman-Sacks disease).

(Ref: Robbins/10th/561)

Comparison of the four major forms of vegetative endocarditis:

1. **Rheumatic fever phase of rheumatic heart disease** is marked by a small, warty vegetations along the lines of closure of the valve leaflets.
2. **Infective endocarditis** is characterized by large, irregular masses in the valve cusps that can extend into the chordae.
3. **Non-bacterial thrombotic endocarditis (NBTE)** typically exhibit small, bland vegetations, usually attached at the line of closure. One or many may be present.
4. **Libman-Sacks endocarditis (LSE)** has small or medium-sized vegetations on either or both sides of the valve leaflets.

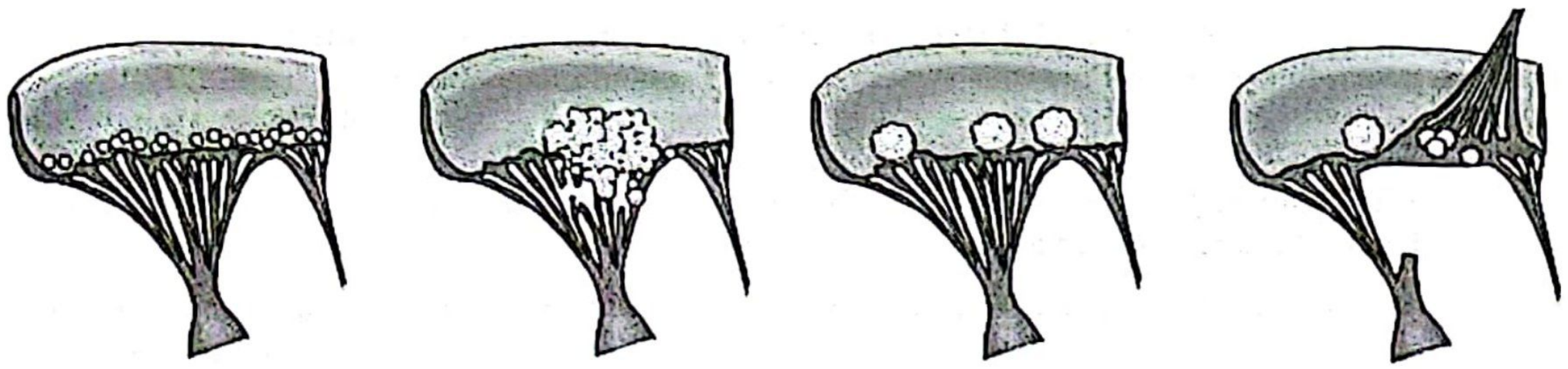


Fig: Diagrammatic comparison between the vegetative heart diseases.

(Ref: Robbins/10th/562)

Q. What is vegetation? (DU-19M)

Ans.

Vegetation: Vegetation in cardiac tissue may be defined as complex of **thrombotic debris** and **organisms,** often resulting from **colonization** or **invasion** of the heart valves or the mural endocardium by a **microbe,** associated with **destruction of the underlying cardiac tissues.**

(Ref: Robbins/10th/563 + 8th/566)

Or,

Thrombi on heart valves are called **vegetations,** which may be **infected** or **sterile.**

(Ref: Robbins/10th/129)

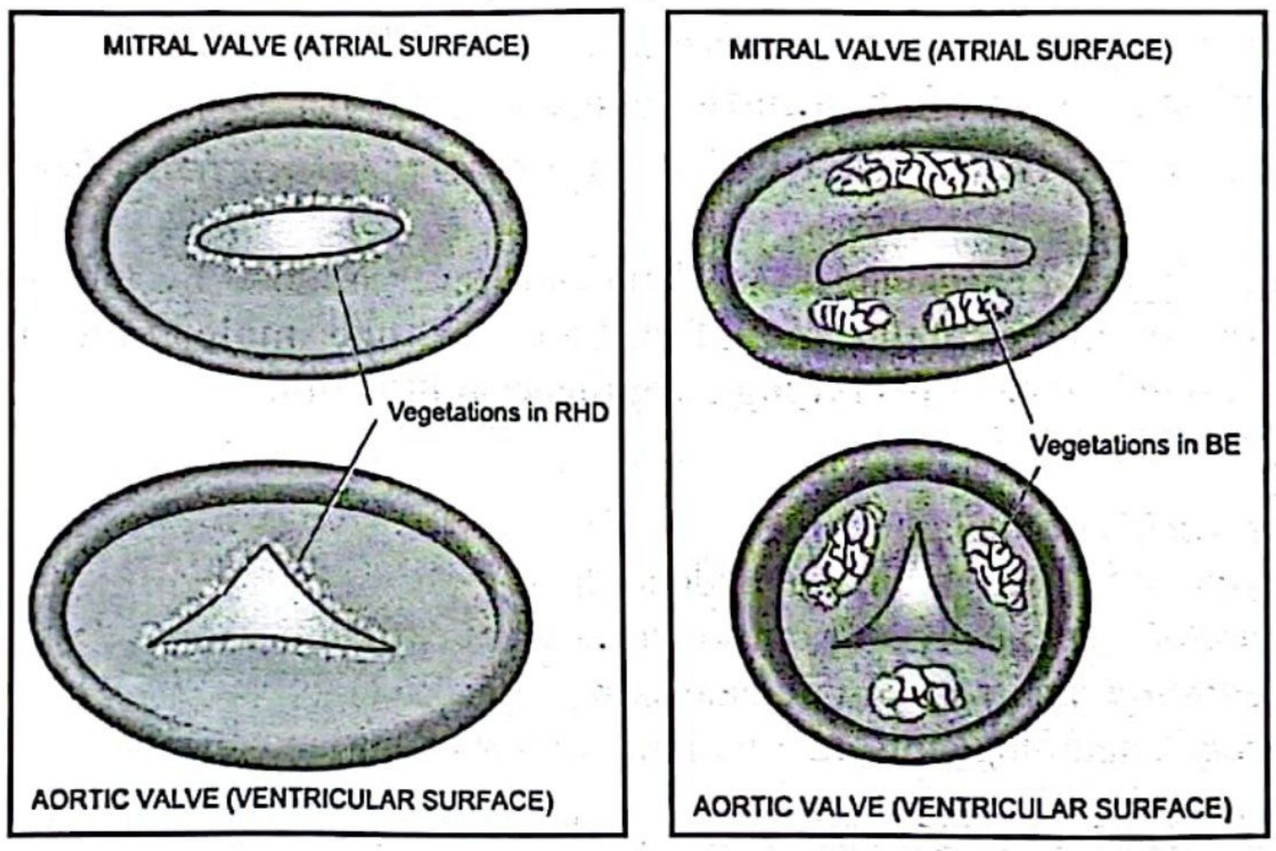


Fig: Location of vegetations on the valves of the left heart (Rheumatic valvulitis in in left image, and infective endocarditis in the right image).

Rheumatic Fever & Rheumatic Heart Disease

Q. What is rheumatic fever? (DU-18Ja, SU-13/08Ja, RU-11Ju, CU-03S)

Q. What is rheumatic heart disease? ***(Very Important for VIVA)***

Q. Which valve is commonly involved in rheumatic fever? (DU-15Ja)

Ans.

Rheumatic fever: Rheumatic fever (RF) is an **acute, immunologically mediated, multisystem inflammatory disease** classically occurring a **few weeks** after **group A streptococcal pharyngitis;** occasionally, can follow **streptococcal infections** at other sites, such as the **skin.**

(Ref: Robbins/10th/560)

Or,

Rheumatic fever (RF) is a **systemic, post-streptococcal, non-suppurative inflammatory disease,** principally affecting the **heart, joints, central nervous system, skin** and **subcutaneous tissues.**

(Ref: Harsh Mohan/7th/418)

Or,

Rheumatic fever is a **multisystem inflammatory disorder** with **major cardiac manifestations and sequelae,** most often affecting children between **5 and 15 years of age.**

It usually occurs **1 to 4 weeks** after an episode of **pharyngitis** caused by **group A β-hemolytic streptococci.**

(Ref: BRS Pathology/5th/139)

Rheumatic heart disease (RHD): Acute rheumatic **carditis** is a common manifestation of active rheumatic fever (RF) and may progress over time to ***chronic rheumatic heart disease (RHD)***, which is characterized principally by **deforming fibrotic valvular disease,** particularly involving the ***mitral valve.***

(Ref: Robbins/10th/560)

Or,

The **chronic stage of RF** involves all the layers of the heart **(pancarditis)** causing major **cardiac sequelae** referred to as ***rheumatic heart disease (RHD)***.

(Ref: Harsh Mohan/7th/418)

Valves involved in RHD:

- Mitral valve (65%-70% cases)
- Aortic valve (25% cases).

(Ref: Robbins/10th/560)

Q. Write down the diagnostic criteria of rheumatic fever. (BUP-22M)
Q. What are the criteria for diagnosis of rheumatic fever? (DU-18Ja,12Ju, SU-17M)
Q. Enumerate the major criteria of rheumatic fever. (CU-19Nv)
Q. Short note: Jones criteria. (DU-23M, CU-15/13Ja) ***(Very Important for VIVA)***

Ans.

Diagnosis of rheumatic fever: The diagnosis of rheumatic fever is done by the so-called **revised Jones criteria,** based on **two or more major manifestations,** or **one major and two or more minor manifestations,** along with **evidence of preceding streptococcal infection.**

Major manifestations:

1. ***Migratory polyarthritis*** of the large joints
2. ***Pancarditis*** (myocarditis, pericarditis, or endocarditis)
3. ***Subcutaneous nodules*** (typically on extensor surfaces of extremities)
4. ***Erythema marginatum,*** an irregular circinate skin rash
5. ***Sydenham chorea,*** a neurologic disorder with involuntary rapid movements

Minor manifestations: Nonspecific signs and symptoms that include-

1. Fever
2. Arthralgia
3. Raised ESR or C-reactive protein (CRP)
4. Previous rheumatic fever
5. Leukocytosis
6. First-degree AV block {Prolonged P-R interval in ECG}

Supporting evidence of preceding streptococcal infection:

1. Recent scarlet fever
2. Raised anti-streptolysin O (ASO) or other streptococcal antibody titer
3. Positive throat culture.

(Ref: Robbins/10th/562; Davidson's/23rd/515; BRS Pathology/5th/140)

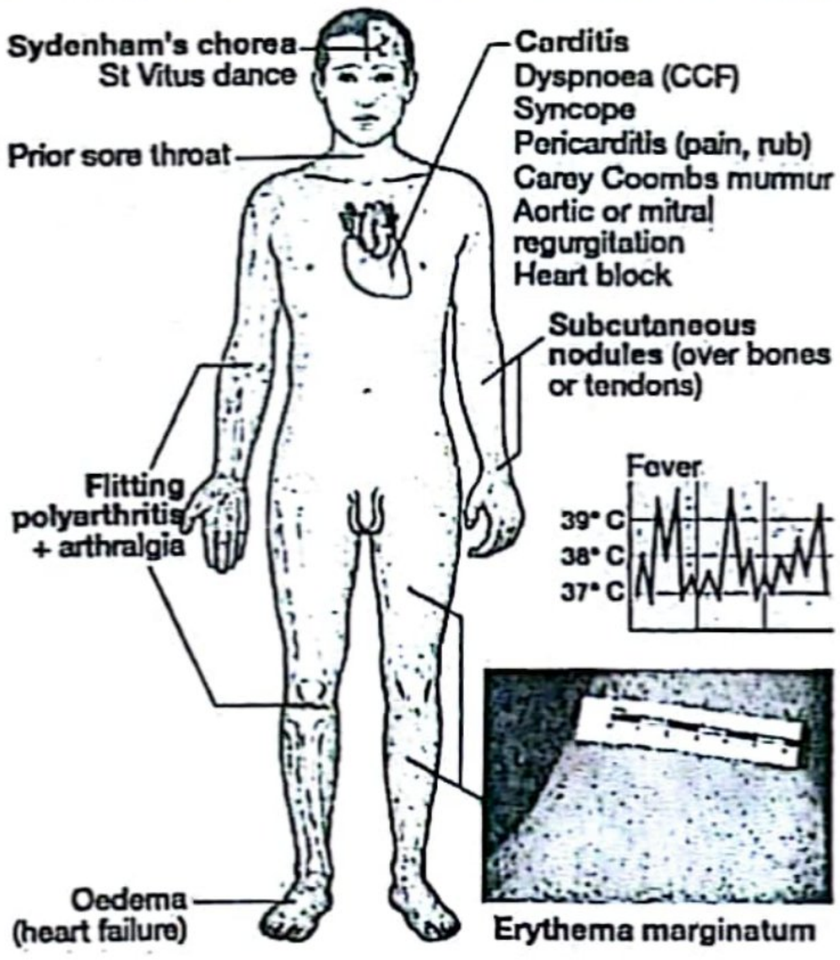


Fig: Clinical features of rheumatic fever. Bold labels indicate Jones major criteria.

Very Very Important for VIVA

1. **Pancarditis:** Inflammation of the pericardium, myocardium, and endocardium.
2. **Joint involvement**
   - **Arthralgia:** Joint pain without clinically evident inflammation.
   - **Arthritis:** Overt joint inflammation presenting as painful, red, swollen, hot joints, usually involving larger joints, especially the knees, ankles, wrists, and elbows.
   - **Migratory polyarthritis** (most common major manifestation of RF): Sequential involvement of multiple joints.
3. **Skin lesions**
   - **Subcutaneous nodules** - small painless swellings usually over bony prominences.
   - **Erythema marginatum** - a distinctive skin rash characteristic of rheumatic fever, often involving the trunk and extremities.
4. **Sydenham chorea (rheumatic chorea)**, also known as **St Vitus dance:** A late neurological manifestation characterized by rapid, purposeless involuntary movements of the hands, feet or face. It appears at least 3 months after the episode of acute rheumatic fever, when all the other signs may have disappeared.

(Ref: BRS Pathology/5th/140; Robbins/10th/562; Davidson's/23rd/515)

Q. Write down the pathogenesis of rheumatic fever. (DU-18/15Ja,11/12Ju, RMU-23/22/18M,15/11Ju,07Ja, SU-17M, CU-11Ja)

Q. Discuss the etiopathogenesis of rheumatic heart disease. (RU-20M)

Q. Write the etiopathogenesis of rheumatic fever. (SU-13Ja)

Ans.

Pathogenesis of rheumatic fever: Rheumatic fever is a **post-infectious immunologic disease** that results from-

i) Cross reaction of the antibodies with host proteins which are produced against streptococcal antigen.
ii) Some forms of autoimmune reaction incited by a streptococcal infection.

A. Cross reaction: The following steps are involved-

Pharyngitis or sore throat by group-A β-haemolytic streptococcus (S. *pyogenes*)
↓
Immune response & formation of antibody against streptococcal antigens (M proteins) after 2-3 weeks
↓
Cross reaction of antibodies with different host tissues e.g. heart valve glycoprotein, myocardial sarcolema, cardiac myosin, joints, and other tissues
↓
Antigen-antibody complex activates complement
↓
Type-II hypersensitivity reaction occurs
↓
Damage to myocardium, heart valve, and other connective tissues

B. <u>Autoimmunity</u>: In some cases, the streptococcal infection can evoke an **autoimmune response** against **cardiac self antigens.**

(Ref: Robbins/10th/561; Microbiology Lecture, SSMC)

Q. Write down the pathology / morphology of rheumatic heart disease. (CU-03S, SU-03S/Ja)

Ans.

<u>Pathology / morphology of rheumatic heart disease</u>: *(Important for VIVA)*

A) ***<u>Morphology of acute rheumatic heart disease</u>:***

- During acute rheumatic fever, ***focal inflammatory lesions*** are found in various tissues. They are most distinctive within the ***heart***, where they are called **Aschoff nodules** or **Aschoff bodies.**
- **Aschoff bodies** consist of fragmented collagen and fibrinoid material, foci of **lymphocytes** (primarily T-cells), occasional **plasma cells,** ***plump activated macrophages,*** called **Anitschkow cells** (pathognomonic for RF), and occasional **multinucleated giant cells** called **Aschoff cells** or **Aschoff giant cells.**
- Diffuse inflammation and Aschoff bodies may be found in any of the three layers of the heart, causing percarditis, myocarditis, or endocarditis (**pancarditis**).
- Inflammation of the endocardium and the left-sided valves typically results in fibrinoid necrosis within the cusps or along the tendinous cords. Overlying these necrotic foci are small (1-2 mm) **vegetations** (fibrin & platelet – ***sterile vegetations***), called **verrucae,** along the lines of closure.

Fig: Acute rheumatic heart disease. Small vegetations (verrucae) are visible along the line of closure of the mitral valve leaflet (arrows).

B) ***<u>Morphology of chronic rheumatic heart disease</u>:***

<u>Macroscopic</u>:

- Leaflet thickening
- Commissural fusion and shortening
- Thickening and fusion of the tendinous cords
- Fibrous bridging across the valvular commissures and calcification create "***fish mouth***" or "***buttonhole***" stenosis.
- Dilatation of left atrium.
- Mural thrombus present in the appendage or along the wall of left atrium.

- Right ventricular hypertrophy due to long-standing lung changes.

Microscopic:
- Diffuse fibrosis and neovascularization in the valvular leaflets.
- Aschoff bodies are replaced by fibrous scar.

(Ref: Robbins/10th/561)

Q. What is Aschoff body? (RMU-22M)
Q. Write the histological findings of Aschoff body. (SU-08Ja)
Q. Short note: Aschoff nodules / Rheumatic nodules. (DU-06M,05Ja, RMU-19M, CU-05Ja)
Ans.

Aschoff body / Aschoff nodules / Rheumatic nodules: ***(Important for VIVA)***

- This is the **classic lesion of rheumatic fever**. During acute rheumatic fever, ***focal inflammatory lesions*** are found in various tissues, but are most distinctive within the ***heart***, where they are called ***Aschoff bodies***.
- **Aschoff bodies** consist of fragmented collagen and fibrinoid material, foci of lymphocytes (primarily T-cells), occasional plasma cells, **plump activated macrophages** called **Anitschkow cells** (pathognomonic for RF) and occasional **multinucleated giant cells** called **Aschoff cells** or **Aschoff giant cells.**

Diffuse inflammation and **Aschoff bodies** may be found in **any of the three layers of the heart**, causing percarditis, myocarditis, or endocarditis (**pancarditis).**

(Ref: Robbins/10th/561; BRS Pathology/5th/139; Harsh Mohan/7th/420)

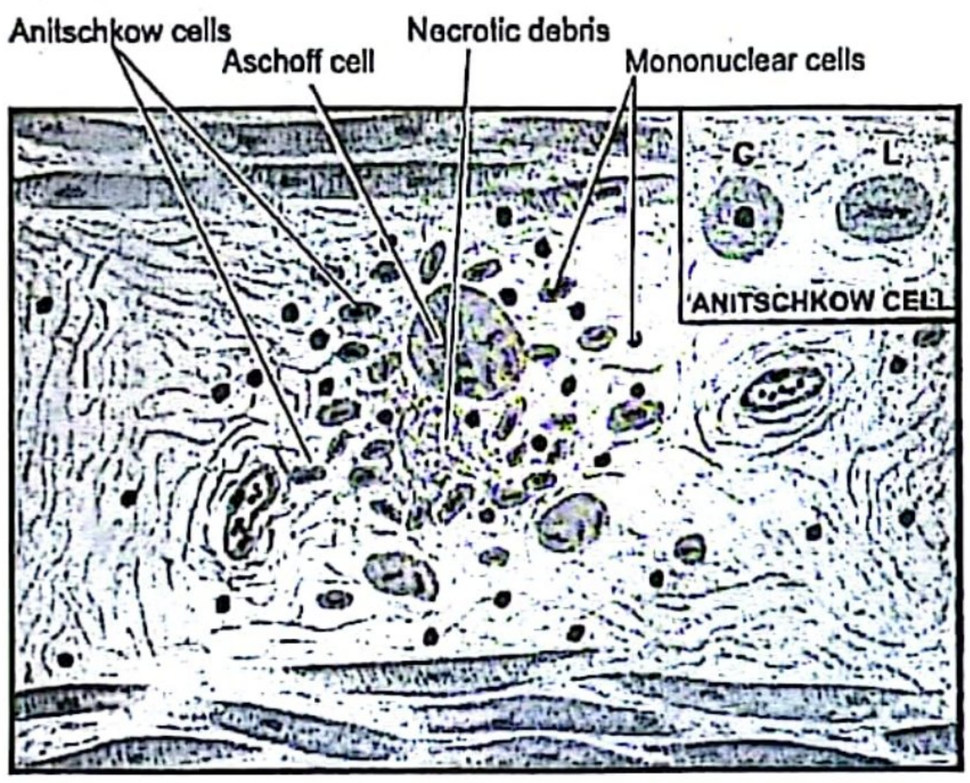


Fig: An Aschoff body (granulomatous stage) in the myocardium. *Inbox* shows Anitschkow cell in longitudinal section (L) with caterpillar-like serrated nuclear chromatin, while cross section (C) shows owl-eye appearance of central chromatin mass and perinuclear halo.

Q. What is anitschkow cell? (RU-18M)
Ans.

Anitschkow cells: Anitschkow cells are ***enlarged macrophages*** found within granulomas (called **Aschoff bodies**) associated with ***rheumatic heart disease*** that have **nuclei** with **central caterpillar-shaped wavy chromatin** in *longitudinal section*, and **owl-eye appearance** of central chromatin mass and **perinuclear halo** in *cross-section*.

(Ref: Robbins/10th/561; Harsh Mohan/7th/420)

(***N.B***: Larger **Anitschkow cells** are **plump activated macrophages** that may coalesce to form **multinucleated Aschoff giant cells**).

Fig: Anitschkow cells.

Q. Write down the cardiac lesions of rheumatic fever. (CMU-21/20Nv)

Ans.

Cardiac lesions of rheumatic fever: Cardiac lesions of RF are in the form of **pancarditis** which is the focal inflammatory involvement of the interstitial tissue of ***all the three layers of the heart*** (endocardium, myocardium and pericardium). The pathognomonic feature of pancarditis in RF is the presence of distinctive ***Aschoff nodules*** or ***Aschoff bodies***.

1. **RHEUMATIC ENDOCARDITIS:** Endocardial lesions of RF may involve the valvular and mural endocardium, causing ***rheumatic valvulitis*** and ***mural endocarditis,*** respectively. Rheumatic valvulitis is chiefly responsible for the major cardiac manifestations in chronic RHD.
2. **RHEUMATIC MYOCARDITIS:** The most characteristic feature of rheumatic myocarditis is the presence of distinctive ***Aschoff bodies***. These diagnostic nodules are scattered throughout the interstitial tissue of the myocardium and are most frequent in the interventricular septum, left ventricle and left atrium.
3. **RHEUMATIC PERICARDITIS:** Inflammatory involvement of the pericardium commonly accompanies RHD. It may manifest as breathlessness or chest pain.

(Ref: Harsh Mohan/7th/420-422; Davidson's/23rd/515)

Q. Enumerate the complications of rheumatic fever. (DU-15Ja,11Ju)

Q. Short note: Complications of rheumatic fever. (RU-18M)

Ans.

Complications of rheumatic fever: ***(Important for VIVA)***

1. Mitral stenosis
2. Cardiac hypertrophy (usually right ventricle)
3. Cardiac dilation
4. Carditis
5. Heart failure
6. Arrhythmias (particularly atrial fibrillation)
7. Thromboembolic complications
8. Infective endocarditis.

(Ref: Robbins/10th/562)

Q. Which valve is most commonly affected in chronic rheumatic heart disease? ***(Important for VIVA)***

Ans.

Mitral valve (indeed, RHD is virtually the only cause of mitral stenosis).

(Ref: Robbins/10th/560; Pathoma Lecture Notes)

Q. What is most common cause of death in acute rheumatic fever? ***(Important for VIVA)***

Ans.

Acute rheumatic myocarditis.

(Ref: Pathoma Lecture Notes)

Q. Short note: Rheumatic fever. (SU-16Ja)
Ans.
Rheumatic fever: *Please write from above.*

Q. A 6 years boy develops fever, joint pain, diffuse skin rash and nodules 3 weeks after recovery from sore throat. His ESR is 70 mm in first hour and ASO titer is 500 IU/ml. What is your probable diagnosis? What are the changes in myocardium and what giant cell is seen there? (DU-14Ju)
Ans.
Probable diagnosis: Acute rheumatic fever.

Changes in myocardium: Area of **focal interstitial inflammation**, called **Aschoff body / aschoff nodule / rheumatic nodule** found in myocardium which is the classic lesion of rheumatic fever. It is characterized by fragmented collagen and fibrinoid material, plump activated macrophages (**Anitschkow cells**), and occasional ***multinucleated giant cells*** (**Aschoff cells / Aschoff giant cells**).

Giant cell: Aschoff cells or Aschoff giant cells.

(Ref: Robbins/10th/561; BRS Pathology/5th/139)

Infective Endocarditis

Q. Classify endocarditis. (SU-13Ju) ***(For VIVA)***
Ans.
Endocarditis: Endocarditis is an **inflammation of the inner layer (endocardium) of the heart.** It usually involves the heart valves, and is characterized by a prototypic lesion, the **vegetation.**

Classification of endocarditis: Based on etiology-

1. **Infective endocarditis:** Microorganisms is the source of inflammation.
2. **Non-infective endocarditis:**
   - Non-bacterial thrombotic endocarditis (NBTE) - most commonly found in previously damaged valves.
   - Libman-Sacks endocarditis (LSE) - occurs more often in patients with SLE.

(Ref: Robbins/10th/563,564)

Q. Classify infective endocarditis. (DU-19M)
Q. Short note: Infective endocarditis. (CU-04S) ***(Important for VIVA)***
Ans.
Infective endocarditis: Infective endocarditis (IE) is a microbial infection of the heart valves or the mural endocardium that leads to the formation of ***vegetations*** composed of thrombotic debris and organisms, often associated with destruction of the underlying cardiac tissues.

(Ref: Robbins/10th/563)

Types:

1. **Acute infective endocarditis** {here the organisms are highly virulent (e.g. *Staphylococcus aureus* (50% of cases)}.
2. **Sub-acute infective endocarditis** {here the organisms are of low virulence, e.g. *viridans streptococci* (more than 50% of cases)}.

(Ref: Robbins/10th/563; BRS Pathology/5th/141)

Causative agents: Although fungi and other classes of microorganisms can be responsible, most nfections are bacterial (***bacterial endocarditis***).

- *Streptococcus viridans* (50-60% cases)
- *Staphylococcus aureus* (20-30% cases)

- HACEK group (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella*)
- *Streptococcus bovis*
- *Streptococcus pneumoniae*
- *Staphylococcus epidermidis*
- Gram-negative enteric bacilli
- Fungi.

(Ref: Robbins/10th/563; Harsh Mohan/7th/425)

Q. What is acute infective endocarditis? *(For VIVA)*

Ans.

Acute infective endocarditis (ABE): *Acute infective endocarditis* is typically caused by infection of a **previously normal heart valve** by a **highly virulent organism** (e.g. *Staphylococcus aureus*) that **rapidly** produces **destructive lesions.**

These infections may be difficult to **cure** with antibiotics alone, and **often require surgery.**

(Ref: Robbins/10th/563)

Q. What is sub-acute infective endocarditis? (DU-11Ju) *(For VIVA)*

Ans.

Sub-acute infective endocarditis (SABE): *Subacute infective endocarditis* is typically caused by infection of a **previously damaged** or **otherwise abnormal valve** by an **organism** with **lower virulence** (e.g. *viridans streptococci*) with **overall less destruction.**

In such cases the disease may pursue a protracted course of **weeks to months**, and **cures** can often be achieved with **antibiotics alone.**

(Ref: Robbins/10th/563; Harsh Mohan/7th/425)

Q. Mention the distinguishing features of acute and subacute bacterial endocarditis.

Ans.

Distinguishing features of acute and subacute bacterial endocarditis: *(For VIVA)*

Features	Acute bacterial endocarditis	Subacute bacterial endocarditis
1. Duration	< 6 weeks	> 6 weeks
2. Most common organism	*Staph. aureus*	*Streptococcus viridans*
3. Virulence of organisms	Highly virulent	Less virulent
4. Previous condition of valves	Usually previously normal	Usually previously damaged
5. Lesion on valves	Invasive, destructive, suppurative	Usually not invasive or suppurative
6. Clinical features	Features of acute systemic infection	Splenomegaly Slubbing of fingers Petechiae

(Ref: Robbins/10th/563; Harsh Mohan/7th/425)

Q. Discuss the etiopathogenesis of infective endocarditis. (DU-19M)

Ans.

Etiopathogenesis of infective endocarditis:

A. Etiology:

1. Infective agents:

- *Staphylococcus aureus* (most common causative organisms in ABE)
- *Streptococcus viridans* (most common causative organisms in SABE)
- The so-called HACEK group (Haemophilus, Astinobacillus, Cardiobacterium, Eikenella, and Kingella)
- *Streptococcus bovis*
- *Streptococcus pneumoniae*
- *Staphylococcus epidermidis*

- Gram-negative enteric bacilli
- Fungi.

2. Predisposing factors:

b. Bacteraemia, septicaemia and pyaemia: Some of the common examples are-

- Periodontal infections such as trauma from vigorous brushing of teeth, hard chewing, tooth extraction and other dental procedures.
- Infections of the bowel, biliary tract and genitourinary tracts
- Surgery of the bowel, biliary tract and genitourinary tracts
- Skin infections such as boils, carbuncles and abscesses.
- Upper and lower respiratory tract infections including bacterial pneumonias
- Intravenous drug abuse

c. Underlying heart disease

- Chronic rheumatic valvular disease (in about 50% cases)
- Congenital heart diseases (e.g. VSD, subaortic stenosis, pulmonary stenosis, bicuspid aortic valve, coarctation of the aorta, and PDA)
- Other causes are syphilitic aortic valve disease, atherosclerotic valvular disease, floppy mitral valve, and prosthetic heart valves.

d. Impaired host defenses

- Neutropenia
- Immunodeficiency
- Malignancy
- Therapeutic immunosuppression
- Diabetes mellitus
- Alcohol or intravenous drug abuse.

B. <u>Pathogenesis</u>: Organisms causing infective endocarditis on **entering the blood stream** from any of the above-mentioned routes are **implanted on the cardiac valves** or **mural endocardium** because they have **surface adhesion molecules** which mediate their **adherence to injured endocardium.**

(Ref: Robbins/10th/563; Harsh Mohan/7th/425)

Q. What are the complications of infective endocarditis? (DU-19M)

Ans.

<u>Complications of infective endocarditis</u>: *(Very Important for VIVA)*

A. Cardiac complications:

- Valvular stenosis or insufficiency
- Perforation, rupture, and aneurysm of valve leaflets
- Abscesses in the valve ring (**ring abscess**)
- Myocardial abscesses
- Suppurative pericarditis
- Cardiac failure from one or more of the foregoing complications.

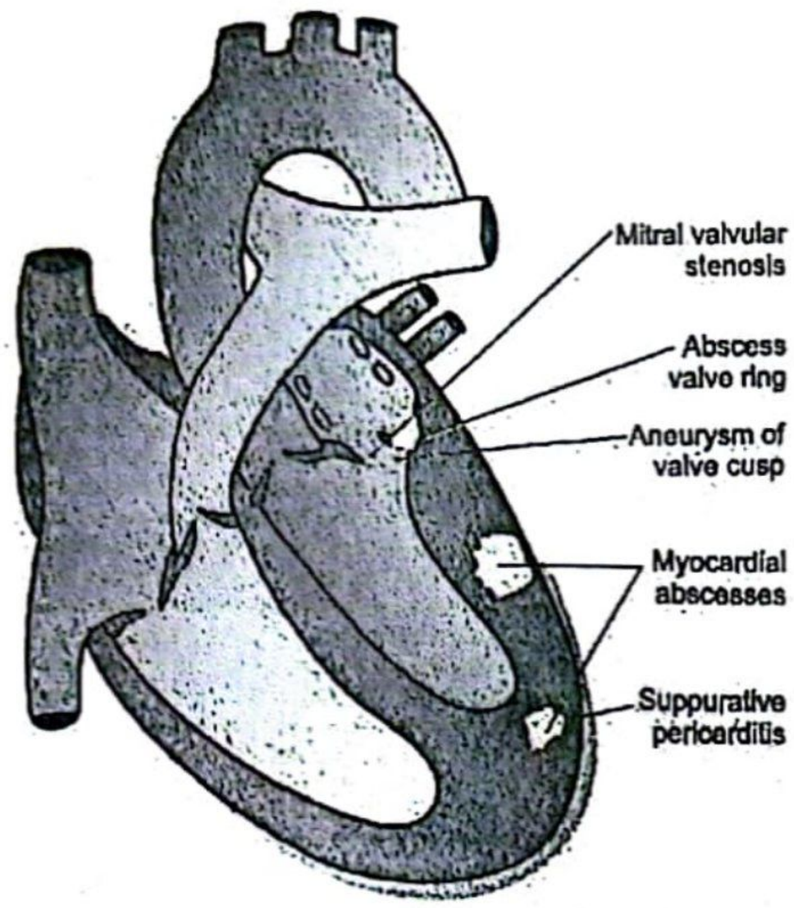
B. Extracardiac complications:

- *Systemic emboli* may cause infarcts & abscess in the brain, kidneys, spleen & lung.
- *Petechiae* may be seen in the skin and conjunctiva.
- *Osler's nodes* in SABE (painful, tender nodules on the finger tips of hands and feet) & *Janeway's spots* in ABE (painless, non-tender subcutaneous maculopapular lesions on the pulp of the fingers)
- *Glomerulonephritis* (due to deposition of antigen-antibody complex in the glomerulus).

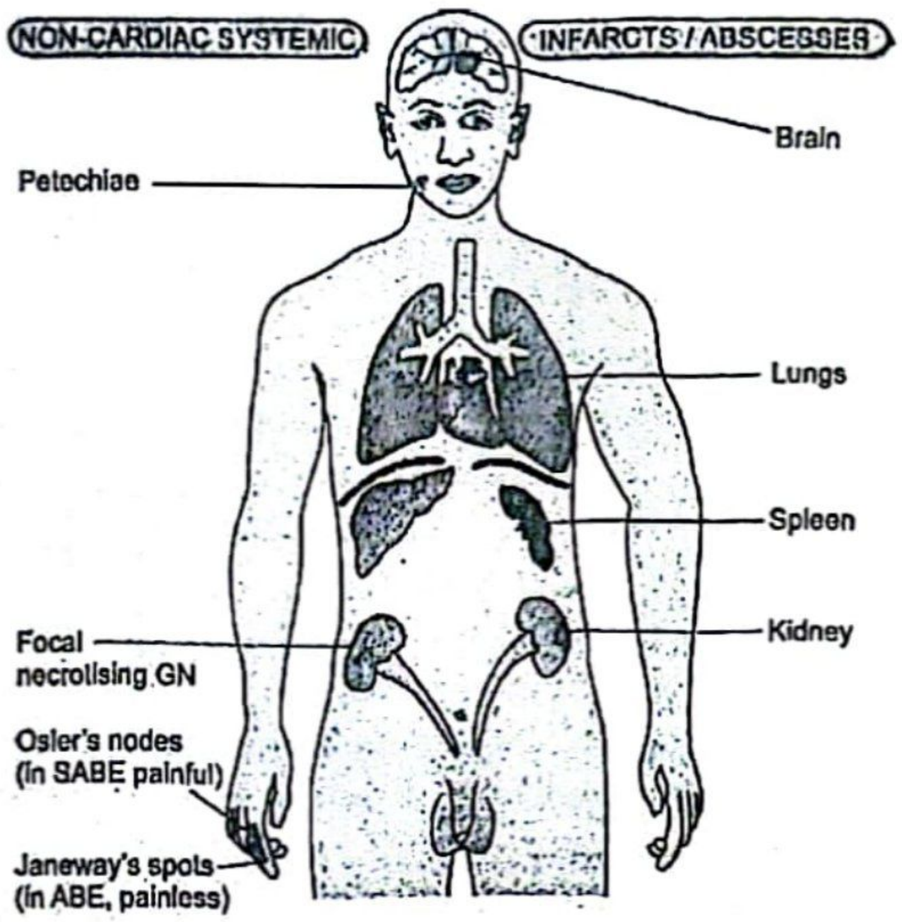
(Ref: Robbins/10th/564; Harsh Mohan/7th/428)

(***N.B***: The ***causes of death*** are cardiac failure, persistent infection, embolism to vital organs, renal failure and rupture of mycotic aneurysm of cerebral arteries.)

(Ref: Harsh Mohan/7th/428)



A, CARDIAC SEQUELAE OF INFECTIVE ENDOCARDITIS



B, EXTRA-CARDIAC COMPLICATIONS

Cardiomyopathy

Q. Define cardiomyopathy. Mention its type. (CU-04S)

Ans.

Cardiomyopathies: The term **cardiomyopathy** (literally, **heart muscle disease**) is used to describe any **cardiac dysfunction** resulting from a **myocardial abnormality**.

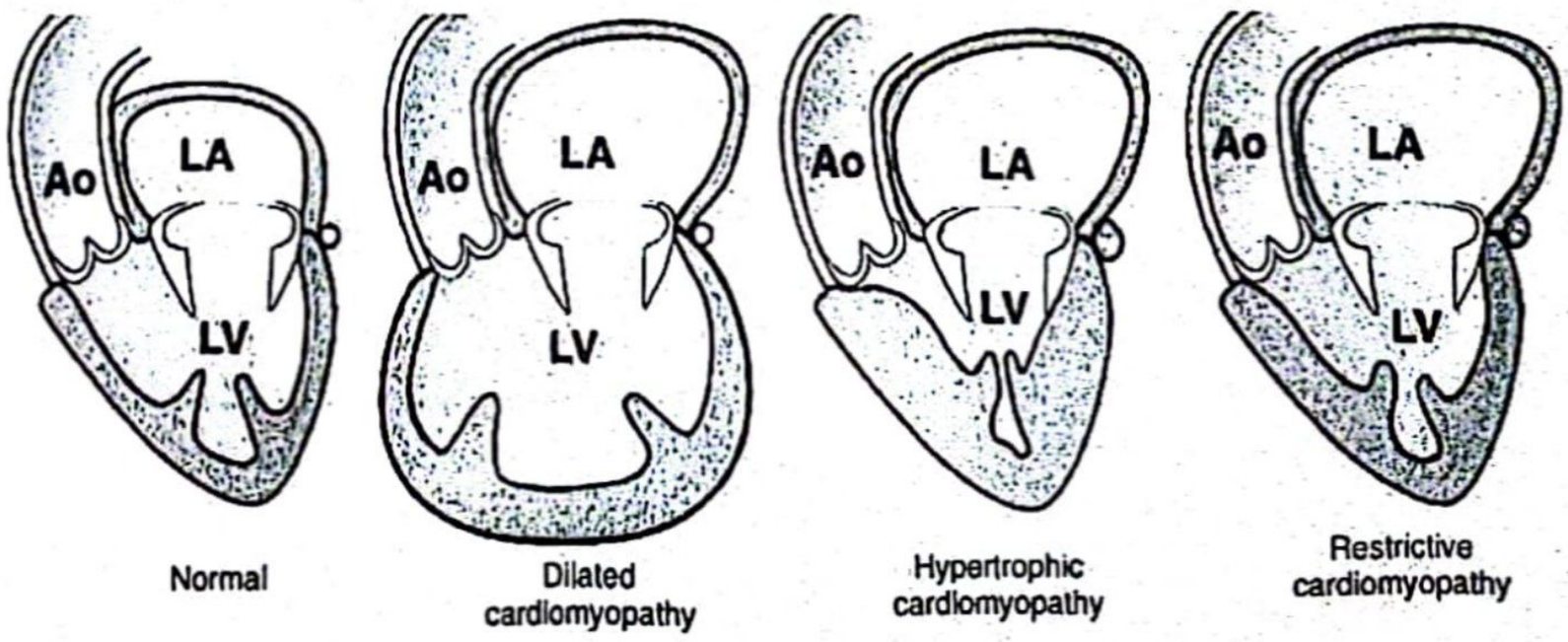
Types: There are two major groups of cardiomyopathies:

1. ***Primary cardiomyopathies*** involve predominantly the heart. They may be genetic or acquired (e.g. viral myocarditis, anthracycline cardiotoxic).
2. ***Secondary cardiomyopathies*** have myocardial involvement as a component of a systemic or multiorgan disorder (e.g. hemochromatosis, amyloidosis).

According to anatomic abnormalities, cardiomyopathies can be classified into three distinct pathologic patterns:

1. Dilated cardiomyopathy (DCM) (including arrhythmogenic cardiomyopathy) – most common (90% of cases)
2. Hypertrophic cardiomyopathy
3. Restrictive cardiomyopathy.

(Ref: Robbins/10th/567)



Q. What is myocarditis? Enumerate the causes of myocarditis.

Ans.

Myocarditis: Myocarditis is a diverse group of pathologic entities in which infectious microorganisms and/or a primary inflammatory process cause myocardial injury.

(Ref: Robbins/10th/575)

Major causes of myocarditis: ***(For VIVA)***

1. **Infections:**
   - Viruses (e.g. coxsackievirus, Echo virus, influenza, HIV, cytomegalovirus)
   - Chlamydiae (e.g. *Chlamydia psittaci*)
   - Rickettsiae (e.g. R. *typhi*, typhus fever)
   - Bacteria (e.g. C. *diphtheriae*, N. *meningitidis*, Borrelia (lyme disease)
   - Fungi (e.g. Candida)
   - Protozoa (e.g. Trypanosoma, Chagas disease, toxoplasmosis)
   - Helminths (e.g. Trichinosis)
2. **Immune-mediated reactions:**
   - Post-viral
   - Post-streptococcal (rheumatic fever)
   - Systemic lupus erythematosus (SLE)
   - Drug hypersensitivity (e.g. methyldopa, sulfonamides)
   - Transplant rejection
   - Immune checkpoint inhibitor therapies
3. **Unknown:**
   - Sarcoidosis
   - Giant cell myocarditis.

(Ref: Robbins/10th/575)

Q. Define and classify pericarditis. (SU-05Ja)

Ans.

Pericarditis: Inflammation of the pericardium is called pericarditis.

It may occur secondary to a variety of cardiac, thoracic, or systemic disorders, metastases from remote neoplasms, or cardiac surgical procedures.

Classification: Two types-

A) Acute pericarditis:

1. Serous pericarditis
2. Fibrinous & serofibrinous pericarditis (*most frequent type*)
3. Purulent or suppurative pericarditis
4. Haemorrhagic pericarditis
5. Caseous pericarditis

B) Chronic or healed pericarditis:

1. ***Adhesive mediastino-pericarditis*:** The pericardial sac is obliterated, and adherence of the external aspect of the parietal layer to surrounding structures produces a great strain on cardiac function.
2. ***Constrictive pericarditis*:** The heart may be encased in a dense, fibrous or fibrocalcific scar that limits diastolic expansion and seriously restricts cardiac output, resembling restrictive cardiomyopathy.

(Ref: Robbins/10th/577)

Q. Enumerate the causes of pericarditis.

Ans.

Causes of pericarditis:

1. **Infectious agents:**
   - Viruses

- Pyogenic bacteria
- Tuberculosis
- Fungi
- Other parasites

2. **Presumably immunologically mediated:**
   - Rheumatic fever
   - Systemic lupus erythematosus (SLE)
   - Scleroderma
   - Post-cardiotomy
   - Post-myocardial infarction (Dressler) syndrome
   - Drug hypersensitivity reaction

3. **Miscellaneous:**
   - Myocardial infarction
   - Uremia
   - Following cardiac surgery
   - Neoplasia
   - Trauma
   - Radiation.

(Ref: Robbins/10th/577)

Q. Give an account of constrictive pericarditis. (SU-05Ja)

Ans.

Constrictive pericarditis: The heart may be encased in a dense, fibrous or fibrocalcific scar that limits diastolic expansion and seriously restricts cardiac output, resembling restrictive cardiomyopathy.

A well-defined history of a previous pericarditis may or may not be present.

In constrictive pericarditis, the pericardial space is obliterated, and the heart is surrounded by a dense, adherent layer of scar with or without calcification, often 0.5 - 1.0 cm thick, that can resemble a plaster mold in extreme cases **(concrétio cordis).**

(Ref: Robbins/10th/578)

Tumours of the Heart

Q. Name the tumours of the heart. ***(For VIVA)***

Ans.

Tumours of the heart:

1. **Primary cardiac tumors:**
   - **Benign:**
     - Myxoma (most common primary tumour of the adult heart)
     - Fibroma
     - Lipoma
     - Papillary fibroelastoma
     - Rhabdomyoma
   - **Malignant:**
     - Sarcoma (angiosarcoma).
2. **Secondary or metastatic neoplasms** (most frequently from lung and breast carcinomas, melanomas, leukemias, and lymphomas).

(Ref: Robbins/10th/527-580)

CHAPTER 03

DISEASES OF WBC, LYMPH NODES, SPLEEN AND THYMUS

Lymphadenopathy

Q. Define generalized lymphadenopathy. (CU-08Ja) **Write down the causes of generalized lymphadenopathy.** (DU-12/07Ja, RU-20/18Nv)
Q. What are the causes of lymphadenopathy? (BUP-22Nv, CU-20M,11/10/08Ju, SU-14/13Ja,11/08Ju, RU-17/16/15/13/12/08Ju)
Q. Enumerate the important causes of generalized lymphadenopathy. (DU-18/17Nv,16Ju, CU-08Ja)
Q. Write down the causes of lymph node enlargement. (RU-07a)
Q. Short note: Lymphadenopathy. (DU-22Nv, RU-09Ju)
Ans.
Generalized lymphadenopathy: When 2 or more groups of lymph nodes are enlarged, the condition is called generalized lymphadenopathy.

Causes of generalized lymphadenopathy: ***(Important for VIVA)***

1. **Infection:**
   - **Viral** - Infectious mononucleosis, CMV, AIDS
   - **Bacterial** - Disseminated tuberculosis, brucellosis, cat scratch disease
   - **Spirochaetal** - Secondary syphilis
   - **Protozoal** - Toxoplasmosis
   - **Helminthic** - Filariasis
   - **Fungal** - Histoplasmosis, coccidioidomycosis
2. **Malignant disease:**
   - Lymphoma
   - Leukaemia
3. **Collagen disease:**
   - Systemic lupus erythematosus (SLE)
   - Rheumatoid arthritis

4. **Miscellaneous:**
   - Sarcoidosis
   - Thyrotoxicosis
   - Drugs- e.g. phenytoin.

(Ref: Medicine Lecture SSMC; de Gruchy/5th/280)

Q. What are the causes of cervical lymphadenopathy? (DU-05M, RU-03M)
Q. A 13 years old boy came with cervical lymphadenopathy. What is your differential diagnosis? (RU-10Ju)
Ans.

Causes of cervical lymphadenopathy:

1. **Inflammation:**
   - Tonsillitis
   - Pharyngitis
   - Sinusitis
2. **Infections:**
   - Tuberculosis
   - Secondary syphilis
   - Toxoplasmosis
   - Filariasis
   - Infectious mononucleosis
3. **Malignant disease:**
   - Lymphoma
   - Leukaemia
   - Secondary deposits (from nasopharynx, larynx, lungs, thyroid, breast, stomach)
4. **Miscellaneous:** Sarcoidosis.

(Ref: Medicine Lecture SSMC & DMC)

Q. Give your approach to diagnose a case of lympadenopathy. (RU-13Ju)
Ans.

Approach to diagnose a case of lympadenopathy:

Examination:

1. Site
2. Number (single or multiple)
3. Size
4. Consistency
   - Rubbery- Lymphoma
   - Firm & matted - TB
   - Hard - malignancy
   - Stony hard - calcified lymph node
   - Soft, cystic - cold abscess.
5. Tenderness (suggests acute inflammation)
6. Discrete or matted (matted in TB)
7. Fixation to underlying structure or overlying skin (in malignancy)
8. Skin (sinus, ulcer, signs of acute inflammation).

Investigation:

1. CBC, ESR and PBF (to exclude leukaemia, increase of eosinophilia in lymphoma, atypical lymphocyte in infectious mononucleosis and high ESR in TB)
2. Chest x-ray (TB, BHL in lymphoma and lymphatic leukaemia)
3. If TB suspected, perform tuberculin test

4. FNAC or biopsy of LN (biopsy is preferable)
5. Bone marrow biopsy (leukaemia and lymphoma)
6. Other investigations (according to suspicion of cause): Ultrasonography (USG) of abdomen (to observe for hepatomegaly, splenomegaly, para-aortic and other lymphadenopathy, ANA (in SLE).

(Ref: Prof. ABM Abdullah/4th/15)

Tumours of Lymph Node (Lymphoma)

Q. Classify tumours of lymph node. (CU-04Ja)

Ans.

Classification of tumours of lymph node (WHO classification):

1. **B-cell neoplasms**
   - **Precursor** B-cell neoplasm (neoplasm of immature B-cell)
   - **Mature** (peripheral) B-cell neoplasm (neoplasm of mature B-cell)
2. **T-cell neoplasms**
   - **Precursor** T-cell neoplasm (neoplasm of immature T-cell)
   - **Mature** (peripheral) T/NK-cell neoplasm (neoplasm of mature T/NK-cell)
3. **Hodgkin lymphoma / Hodgkin disease** (neoplasms of **Reed-Sternberg cells** and variants)

   A. Classical Hodgkin lymphoma
   - Nodular sclerosis
   - Mixed cellularity
   - Lymphocyte rich
   - Lymphocyte depleted

   B. Non-classical Hodgkin lymphoma
   - Lymphocyte predominant.

(Ref: Robbins/10th/592; BRS Pathology/5th/180)

Q. Define (RU-19/17Nv) **& classify lymphoma (/malignant lymphoma).** (RMU-22Nv,14/12Ju, CU-14Ja,11Ju,08Ja)

Q. Classify lymphoma. (RU-21/20M,17Ja)

Ans.

Lymphoma: Lymphoma may be defined as the **neoplastic proliferation of cells native to the lymph nodes.** The cells are **lymphocytes** and its precursors and **histiocytes** (derived from monocyte).

Classification of lymphoma:

1. **Hodgkin lymphoma:** Malignant neoplasm of **lymph node** characterized by the *presence* of neoplastic giant cells called **Reed-Sternberg (RS) cells** and **pleomorphic infiltration** by lymphocyte, eosinophil, macrophage, plasma cell, neutrophil and follicular dendritic cells.

   WHO classification of Hodgkin lymphoma:

   A. ***Classical Hodgkin lymphoma***
   - Nodular sclerosis
   - Mixed cellularity
   - Lymphocyte rich
   - Lymphocyte depleted

   B. ***Non-classical Hodgkin lymphoma*** (classic RS cells absent or rare)
   - Lymphocyte predominant.

2. **Non-Hodgkin lymphoma:** Malignant neoplasm of lymph node characterized by **monomorphic infiltration** and *absence* of **RS (Reed-Sternberg) cells.**

Classification of Non-Hodgkin lymphoma:

C. **REAL classification:** *Please see below.*
D. **Working classification:** *Please see below.*

(Ref: Robbins/10th/611; BRS Pathology/5th/179)

Q. What is R-S cell? (DU-18/17Nv, RMU-23M, CU-13Ja)
Q. Describe a typical RS cell. (DU-14Ju, RU-16Ju,07Ja)
Q. What are the variants of Reed-Sternberg (RS) cells? (DU-15/14Ju)
Q. Write the types of Reed-Sternberg cells. (CU-14Ja)
Q. Give the morphology of classical R-S cells and variants. (DU-23/17M,16Ju)
Q. Describe the morphology of Reed-Sternberg (RS) giant cell. (DU-11Ja, RU-20M,17Ju, CU-10Ja)
Q. Draw and label Reed-Sternberg (RS) cell. (RU-10Ju)
Q. Short note: Reed-Sternberg (R-S) giant cell. (DU-22Nv,21Ja,20Nv/M,17/16Ja,12Ju,09/08/06Ja, SUST-21Nv,06M, CMU-21M; RU-19M,12Ja,09Ju)

Ans.

Reed-Sternberg (R-S) cells: These are the **malignant lymphoid cells** of **B-cell origin** which is the **hallmark** of ***Hodgkin's disease.***

Classic (typical) RS cell is a large cell (tumour giant cell) - (45 µm in diameter) characterized by:

- ***Bi-lobed nucleus***, with two halves often appearing as ***mirror images*** of each other.
- Each nucleus contains a large ***inclusion-like nucleolus*** surrounded by a ***clear zone (halo)*** imparting an **'owl-eye'** appearance.
- The nucleus is surrounded by non-malignant T-lymphocytes, plasma cells and abundant eosinophilic cytoplasm.

Fig: Typical R-S cell.

RS cells may be present in some other conditions, such as:

- Infectious mononucleosis
- Non-Hodgkin lymphoma
- CLL.

Several variants of RS cells:

1. **Mononuclear variants:** It contains a ***single nucleus*** with a large inclusion-like nucleolus.

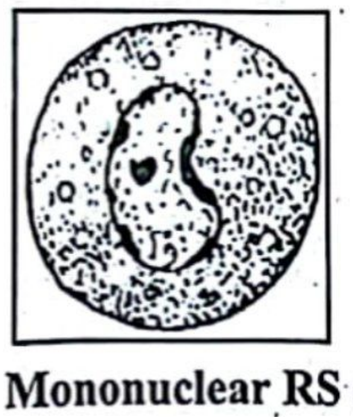


Fig: Mononuclear RS cell.

2. **Lacunar cells:** Have ***single multilobate nucleus***, multiple small nucleoli, and abundant, pale-staining cytoplasm. In sections of formalin-fixed tissue, the cytoplasm often is torn away, leaving the nucleus lying in an empty space (a ***lacune***).

Fig: Lacunar RS cell.

3. **Lympho-histiocytic variants:** Have ***delicate multilobed***, puffy nucleus with abundant pale cytoplasm resembling popped corn (**"popcorn cell"**). Found in lymphocyte-predominant Hodgkin lymphoma.

Fig: L&H variant of RS cells (abundant pale cytoplasm with 'popcorn' nucleus).

(Ref: Robbins/10th/612; Basic Hematology, Dr. Mainuddin/71; BRS Pathology/5th/179)

Q. Classify Hodgkin's lymphoma. (DU-15Ju,13/11Ja, RMU-19Nv, SU-19Nv, CU-13Ja)
Q. Classify Hodgkin's disease in brief. (RU-18Nv,10Ju, SU-11/10/09/06Ja)
Q. State the subtypes of Hodgkin's lymphoma with basic morphological features. (CMU-22M)
Q. Mention histological types of Hodgkin's disease with key features. (CU-19M,12Ju)
Q. Give the morphological findings of Hodgkin's disease. (RU-18Nv, CU-13Ju)
Q. Give the microscopic findings of mixed cellular Hodgkin's disease. (SU-11Ju,10Ja, CU-08Ja)
Q. Write the morphology (histological features) of nodular sclerosis type Hodgkin's lymphoma. (SU-22/20Nv,19Nv/M,09/06Ja)
Q. Write the WHO classification of Hodgkin's lymphoma. (DU-17M,14Ju, SU-22Nv,.CU-10Ja)
Q. Short note: Nodular sclerosis variety of Hodgkin's disease. (DU-09Ju, SU-11/09/06Ja)
Q. Short note: Hodgkin's lymphoma. (DU-19Nv, CU-16/15Ja, SU-07Ja)
Q. Short note: Hodgkin's disease. (RU-18M)

Ans.

Hodgkin lymphoma: Malignant neoplasm of ***lymph node*** characterized by the ***presence*** of **neoplastic giant cells** called **Reed-Sternberg cells (RS cells)** and ***pleomorphic infiltration*** by lymphocyte, eosinophil, macrophage, plasma cell, neutrophil and follicular dendritic cells.

Criteria:

- Characteristically affects ***young adults*** (**20-40** age groups).
- ***Males*** are affected ***twice as commonly as female.***
- Arises in a ***single node*** or ***group of nodes*** and spreads first to anatomically **contiguous** lymphoid tissues.
- Histological hallmark is ***presence of RS (Reed-Sternberg) cells.***

Clinical features:

- May be ***asymptomatic.***
- May present with ***painless peripheral lymphadenopathy*** (usually **rubbery** and **discrete**, but may become **matted**)
- ***Hepatosplenomegally***
- ***Systemic features*** ('B' symptoms): Fever (**Pel-Ebstein** fever), night sweats, weight loss, pruritus.

Classification (WHO classification): ***(V.V.I for VIVA)***

A. **Classical Hodgkin lymphoma** (95% of cases)
   - Nodular sclerosis
   - Mixed cellularity
   - Lymphocyte rich
   - Lymphocyte depletion

B. **Non-classical Hodgkin lymphoma** (5% of cases) – classic RS cells absent or rare
   - Lymphocyte predominant.

Morphology:

- Neoplastic giant cells (**RS cells**) is the **true neoplastic element** in Hodgkin disease.
- Diagnostic (typical) RS cells are large cells with ***bi-lobed nucleus***, with two halves often appearing as ***mirror images*** of each other. Each nucleus contains a large ***inclusion-like nucleolus*** surrounded by a ***clear zone (halo)*** imparting an '**owl-eye**' appearance. The nucleus is surrounded by non-malignant T-lymphocytes, plasma cells and abundant eosinophilic cytoplasm.
- They are positive for CD15 & CD30, but are negative for CD45.

(Ref: Robbins/10th/611; Hoffbrand Haematology/6th/246; de Gruchy/5th/281)

Subtypes of Hodgkin's lymphoma:

Subtype	Morphology
Nodular sclerosis (65-70%). ▪ Most common form ▪ Occurs more frequently in young women	▪ Lymph nodes show prominent **fibrous bands** leading to nodular architecture ▪ A characteristic **lacunar cell** variant of the RS cell is often found ▪ Lacunar cell has a single multilobate nucleus, multiple small nucleoli, and abundant, pale-staining cytoplasm ▪ Background infiltrate composed of T lymphocytes, eosinophils, macrophages and plasma cells
Mixed cellularity (20-25 %)	▪ **Classic RS cells** are ***plentiful*** ▪ Background infiltrate rich in T-lymphocytes, eosinophils, macrophages and plasma cells
Lymphocyte rich (5%)	▪ ***Scanty*** **RS cells** ▪ Background infiltrate ***rich in T-lymphocytes*** with few eosinophils and plasma cells
Lymphocyte depleted (rare)	Few lymphocytes, numerous R-S cells and extensive necrosis and fibrosis
Lymphocyte predominant (5%)	▪ Frequent **lympho-histiocytic (L&H) variant of RS cells** or "**popcorn cells**" are characteristic. These have a delicate multilobed, puffy nucleus with abundant pale cytoplasm resembling popcorn. ▪ **Classic RS cells are absent or rare.**

(Ref: Robbins/10th/613; BRS Pathology/5th/179-182; Hoffbrand Haematology/6th/248)

{N.B: Lymphocyte predominant (non-classical) Hodgkin lymphoma does not show classic RS cells and has many features of Non-Hodgkin's lymphoma and may be treated as such}.

(Ref: Hoffbrand Haematology/6th/247)

Q. Classify non-Hodgkin's lymphoma according to Working classification. (SU-14Ja,13Ju/Ja, 08Ju)

Q. Short note: Non-Hodgkin's lymphoma. (RU-17NV)

Ans.

Non-Hodgkin's lymphoma (NHL): Malignant neoplasms of ***lymphoid cells*** or ***other cells native to lymphoid tissue*** characterized by monoclonal proliferation of lymphoid cells of ***B-cell (85%)*** and ***T/NK-cell (15%)*** origin.

Criteria:

- May arise at ***any age*** (peak incidence is 65-70 years).
- ***Males*** are affected ***twice as commonly as female.***
- Usual presentation is ***localized*** or ***generalized peripheral lymphadenopathy***, which are ***discrete, painless*** and ***firm.***
- Spreads rapidly to ***non-contiguous*** areas.
- Involvement of ***mesenteric,*** oropharyngeal lymphoid structures (***Waldeyer's ring***) and ***epitrochlear lymph nodes*** is very much common.
- ***Extranodal involvement*** is also ***common*** e.g. bone marrow, GIT, stomach, lung, thyroid, skin, testis, CNS etc.
- ***Systemic features*** are generally ***less common.***
- Histological hallmark is ***absence*** of ***RS (Reed-Sternberg) giant cells.***

Etiology:

- **Unknown** in majority of cases.
- **Infectious agents,** e.g. **virus** (HTLV-1, EBV, HHV-8, HIV-1, HCV), **bacteria** (*H. pylori* – causes gastric lymphoma), **protozoa** (malaria – causes Burkitt lymphoma).

Classification of non-Hodgkin's lymphoma: There are various classifications in the field of NHL:

1. REAL classification (*please see below*)
2. Working classification

Working classification: In this classification, NHL is divided into three major prognostic subgroups (depending on the rate at which the cells are dividing)-

1. **Low grade:**
   - **Low** cell proliferation rate.
   - **Asymptomatic** for many years.
   - Slow indolent course.
   - **Incurable,** but the patient survives for long time.
2. **High grade:**
   - **High** cell proliferation rate.
   - **Early symptoms** are common.
   - Fatal, if untreated.
   - Responds better to treatment **(potentially curable** disease).
3. **Intermediate grade.**

Investigations: *Please see below.*

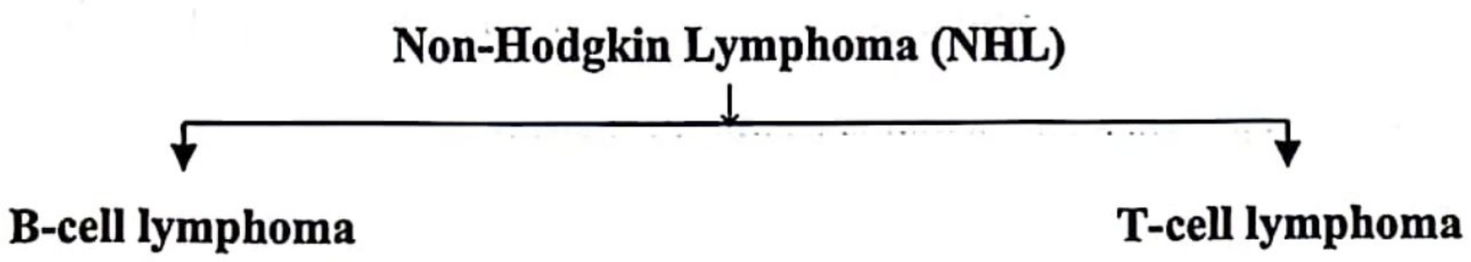
(Ref: Robbins/10th/611; Basic Hematology, Dr. Mainuddin/74; de Gruchy/5th/283; Hoffbrand Haematology/6th/254)

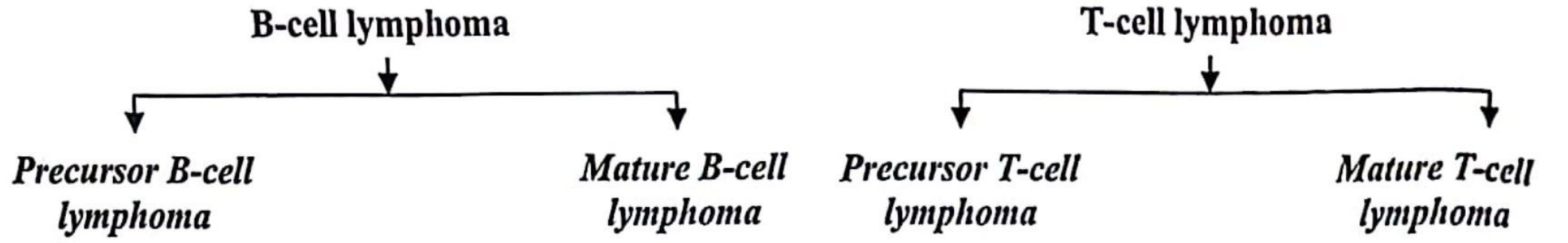
Q. Write down the basis of REAL classification of NHL. (CU-10Ju)
Q. State the WHO classification of NHL. (CU-20Nv)
Ans.

REAL classification (Revised European-American classification of Lymphoid neoplasms) / WHO classification of NHL:

1. Immunophenotype and genetic aberrations
2. Morphologic and clinical features.

REAL classification of NHL:





(Ref: Robbins/10th/592; BRS Pathology/5th/180)

Q. Write down the differences between Hodgkin's & non-Hodgkin's lymphoma. (DU-23M,18Nv,17Nv/M,16/15/14Ju,13/12Ja, CMU-23M,21Nv,20M,19Nv,18M,16Ju,13Ja, SU-22/20Nv, 19M,13Ju, RU-20/19Nv,16/14/10Ju)

Q. Give four main differences of Hodgkin's disease & non-Hodgkin's lymphoma. (DU-11/07Ja, CU-11Ju, SU-09Ju,05Ja)

Q. Give 3 differences between Hodgkin's & non-Hodgkin's lymphoma. (CU-12Ju)

Ans.

Differences between Hodgkin & non-Hodgkin lymphoma: ***(Very Important for VIVA)***

Traits	Hodgkin's lymphoma	Non-Hodgkin's lymphoma
1. Reed-Sternberg (RS) cells	Present (hallmark)	Absent
2. Lymph node involvement	Single axial group of nodes (cervical, mediastinal, para-aortic)	Multiple peripheral nodes
3. Spread	Orderly spread by contiguity	Non-contiguous spread (via blood)
4. Mesenteric nodes & Waldeyer ring	Rarely involved	Commonly involved
5. Epitrochlear LN	Rarely involved	Commonly involved
6. Extra-nodal involvement	Less common	More common
7. Systemic features or B symptoms	More common	Less common
8. Pruritus	More common	Less common
9. Leukaemic transformation	Rare	Common
10. Prognosis	High cure rate	Low cure rate

(Ref: Robbins/10th/611; Davidson's/21st/1039; Basic Hematology, Dr. Mainuddin/76)

Q. Write down the possible investigations to evaluate a suspected case of lymphoma. (CU-18Nv)

Q. How will you diagnose a case of non-Hodgkin's lymphoma (NHL)? (CU-14Ja)

Ans.

Possible investigations to evaluate a suspected case of lymphoma:

1. CBC with ESR and PBF

2. Chest X-ray
3. USG of whole abdomen
4. CT scan of chest, abdomen, pelvis, neck (necessary for staging)
5. PET scan (positron emission tomography)
6. **FNAC** or **biopsy** of lymph nodes (**biopsy is preferable – excisional** or **image guided core needle biopsy**) followed by **histopathology** and **IHC (immunohistochemistry)** – *confirmatory*
7. Bone marrow biopsy (preferably trephine biopsy from unilateral iliac crest)
8. Liver function tests
9. Renal function tests.

(Ref: de Gruchy/5th/285; Hoffbrand Haematology/6th/257; Long Cases in Clinical Medicine/1st/644,648)

Nice to Know:

Clinical staging of Hodgkin's & non-Hodgkin's lymphoma (Ann Arbor classification):

Stage	Distribution of disease
I	Involvement of a single lymph node region (I) or Involvement of a single extralymphatic organ or site (I_E)
II	Involvement of two or more lymph node regions on the same side of the diaphragm alone (II) or Localized involvement of an extralymphatic organ or site (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm without (III) or with (IIIE) localized involvement of an extralymphatic organ or site
IV	Diffuse involvement of one or more extralymphatic organs or sites with or without lymphatic involvement

(Ref: Robbins/10th/615)

{All stages are further divided on the basis of the absence (A) or presence (B) of the following symptoms: unexplained fever, drenching night sweats, and/or unexplained weight loss of greater than 10% of normal body weight.}

(Ref: Robbins/10th/615)

Q. A male aged 20 years presented with multiple, painless, enlarged lymph nodes in cervical and axillary regions. What is your provisional diagnosis? What tests you can do on the lymph nodes to establish the diagnosis? (DU-19M)

Ans.

Provisional diagnosis: Lymphoma.

Tests can be done on the lymph nodes to establish the diagnosis: Lymph node biopsy followed by histopathology & immuno-histochemistry (if needed).

Spleen

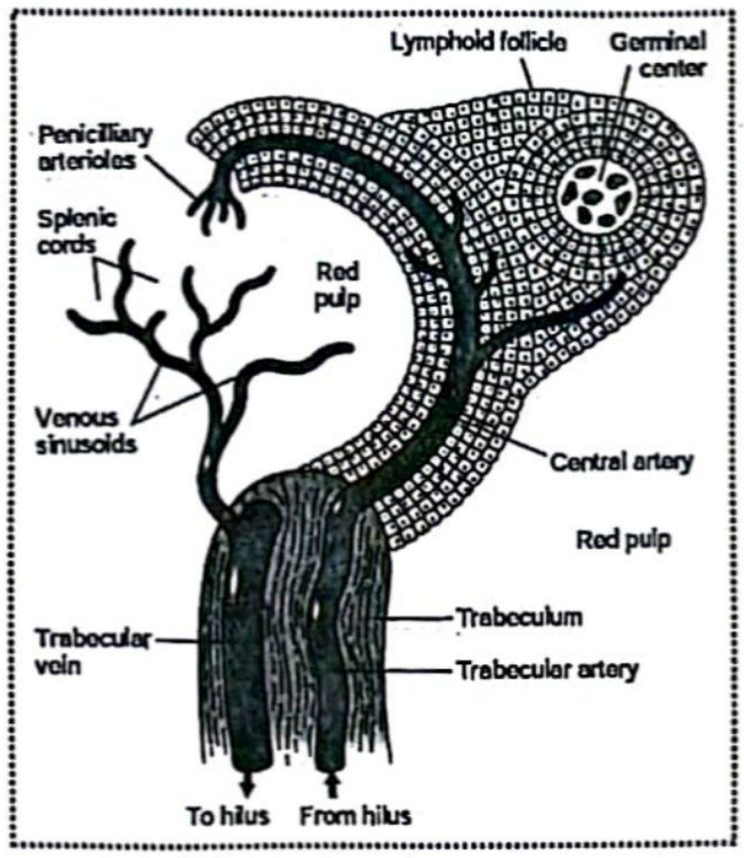


Fig: Normal splenic architecture.

Q. What are the functions of spleen?

Ans.

Functions of spleen:

1. Phagocytosis of blood cells and particulate matter
2. Antibody production
3. Hematopoiesis
4. Sequestration of formed blood elements.

(Ref: Robbins/10th/629)

Q. Mention the causes of splenomegly.

Ans.

Causes of splenomegly:

1. **Infections:**
   - Nonspecific splenitis of various blood-borne infections (particularly infectious endocarditis)
   - Infectious mononucleosis
   - Tberculosis
   - Tphoid fever
   - Brucellosis
   - Cytomegalovirus
   - Syphilis
   - Malaria
   - Histoplasmosis
   - Toxoplasmosis
   - Kala-azar
   - Trypanosomiasis
   - Schistosomiasis
   - Leishmaniasis
   - Echinococcosis
2. **Congestive states related to portal hypertension:**
   - Cirrhosis of liver
   - Portal or splenic vein thrombosis
   - Cardiac failure

3. **Lympho-haematogenous disorders:**
   - Hodgkin lymphoma
   - Non-Hodgkin lymphoma
   - Multiple myeloma
   - Myeloproliferative disorders
   - Haemolytic anaemias
4. **Immunologic-inflammatory conditions:**
   - Rheumatoid arthritis
   - Systemic lupus erythematosus (SLE)
5. **Storage diseases:**
   - Gaucher disease
   - Niemann-Pick disease
   - Mucopolysaccharidoses
6. **Miscellaneous:**
   - Amyloidosis
   - Primary neoplasms and cysts
   - Secondary neoplasms.

(Ref: Robbins/10th/630)

Q. What do you mean by hypersplenism?

Ans.

Hypersplenism: Enlargement of spleen can cause a syndrome known as hypersplenism which is characterized by anaemia, leukopenia, thrombocytopenia, alone or in combination.

The probable cause of the cytopenias is increased sequestration of formed elements and the consequent enhanced phagocytosis by the splenic macrophages.

(Ref: Robbins/10th/629)

For Viva:

Important causes of splenomegaly:

1. Chronic malaria
2. Chronic kala-azar
3. Liver cirrhosis
4. Non-cirrhotic portal hypertension
5. Hemolytic anaemia
6. Leukemia
7. Lymphoma
8. Infectious mononucleosis
9. Systemic lupus erythematosus (SLE).

(Ref: Medicine Lecture SSMC)

Q. What are the causes of massive splenomegally?

Ans.

Causes of massive splenomegally:

1. Chronic myeloid leukaemia (CML)
2. Myelofibrosis
3. Hemolytic anemia
4. Chronic kala-azar
5. Chronic malaria
6. Lymphoma.

(Ref: Medicine Lecture SSMC)

Thymus

Q. Name some disorders of thymus.

Ans.

Disorders of thymus:

1. **Developmental disorders:**
   - Thymic hypoplasia or aplasia is seen in DiGeorge syndrome, accompanied by parathyroid developmental failure
   - Isolated thymic cysts
2. **Thymic hyperplasia:** The term "thymic hyperplasia" is a bit misleading, as it usually applies to the appearance of lymphoid follicles within the thymus, a state that is referred to as *thymic follicular hyperplasia.*
3. **Thymic neoplasms:**
   - Germ cell tumours
   - Lymphomas
   - Carcinoids
   - Thymomas: Tumours of thymic epithelial cells.

(Ref: Robbins/10th/631)

CHAPTER 04

RESPIRATORY SYSTEM

Diseases of the Lungs & Pleura

Q. Name the diseases of respiratory system.
Ans.
Diseases of lungs:

1. **Congenital anomalies:**
   - Pulmonary hypoplasia
   - Foregut cysts
   - Pulmonary sequestration
   - Tracheal and bronchial anomalies (atresia, stenosis, tracheo-esophageal fistula)
   - Vascular anomalies
   - Congenital pulmonary airway malformation
   - Congenital lobar overinflation (emphysema)
2. **Atelectasis (collapse)**
3. **Pulmonary edema**
4. **Acute lung injury & acute respiratory distress syndrome (ARDS)**
5. **Obstructive and restrictive lung diseases: *(Important for VIVA)***
   a) **Obstructive pulmonary diseases**
      - Chronic obstructive pulmonary disease (COPD)
        - Emphysema
        - Chronic bronchitis
      - Asthma
      - Bronchiectasis

b) Chronic diffuse interstitial (restrictive) disease
- Fibrosing diseases, e.g. idiopathic pulmonary fibrosis, pneumoconioses, drug reaction, radiation pneumonitis
- Granulomatous diseases, e.g. sarcoidosis, hypersensitivity pneumonitis
- Pulmonary eosinophilia
- Smoking-related interstitial diseases
- Pulmonary langerhans cell histiocytosis
- Pulmonary alveolar proteinosis
- Surfactant dysfunction disorders

6. Diseases of vascular origin:
- Pulmonary embolism and infarction
- Pulmonary hypertension
- Diffuse pulmonary hemorrhage syndromes

7. Pulmonary infections:
- Pneumonia
- Lung abscess
- Pulmonary TB

8. Lung transplantation

9. Lung tomours:

a. Benign:
- Adenoma
- Fibroma
- Leiomyoma
- Lipoma
- Haemangioma
- Haemangiopericytoma
- Chondroma

b. Malignant:

i. Primary:
- Bronchogenic carcinoma (90-95%)
- Bronchial carcinoid (about 5%)
- Fibrosarcoma
- Leiomyosarcoma
- Hodgkin's and Non-Hodgkin's lymphoma

ii. Secondary (*more common than primary tumors*)**:** Particularly from carcinoma of **breast, colon, kidney, uterus, ovary, testes, thyroid**, and also from **osteogenic** and **other sarcomas.**

c. Tumor like lesion:
- Hamartoma
- Eosinophilic granuloma

<u>Diseases of pleura:</u>

1. Pleural effusion: Inflammatory & non-inflammatory.

2. Pneumothorax

3. Pleural tumors:

a. ***Primary tumours*** *(tumours arising from pleura)*:
- Benign mesothelioma (fibroma)
- Malignant mesothelioma (with heavy exposure to asbestos).

b. ***Secondary / metastatic tumours*** *(most frequantly from lung and breast).*

(Ref: Robbins/10th/673-727; Lecture SSMC)

Q. Mention the causes of haemoptysis. (RU-08Ja)

Ans.

Most common cases of haemoptysis: (For VIVA)

A. INFLAMMATORY

- Bronchitis
- Bronchiectasis
- Pulmonary tuberculosis
- Lung abscess
- Suppurative pneumonia

B. NEOPLASTIC

- Bronchial carcinoma
- Bronchial adenoma

C. OTHERS

- Pulmonary embolism
- Acute left ventricular failure
- Mitral stenosis
- Trauma
- Foreign bodies
- Primary pulmonary hypertension
- Haemorrhagic diathesis.

(Ref: Harsh Mohan/7th/480; Lecture SSMC & DMC)

Atelectasis (Collapse)

Q. Define and describe atelectasis (collapse).

Ans.

Atelectasis (collapse): Atelectasis refers either to incomplete expansion of the lungs (neonatal atelectasis) or to the collapse of previously inflated lung, producing areas of relatively airless pulmonary parenchyma.

Types:

1. **Resorption (or obstruction) atelectasis:** It is the consequence of ***complete obstruction*** of an airway, which in time leads to ***resorption of air*** trapped in the **distal alveoli,** without impairment of blood flow through the affected alveolar walls.

   Here, airway obstruction is most often caused by excessive secretions (e.g. mucus plugs) or exudates within smaller bronchi, as may occur in bronchial asthma, chronic bronchitis, bronchiectasis, and postoperative states. Aspiration of foreign bodies and intrabronchial tumors may also lead to airway obstruction and atelectasis.

2. **Compression atelectasis:** It results whenever significant volumes of **fluid** (transudate, exudate, or blood), **tumor**, or **air** *(pneumothorax)* **accumulate** within the **pleural cavity**.

3. **Contraction atelectasis:** Occurs when focal or generalized **pulmonary** or **pleural fibrosis prevents full lung expansion.**

Significant atelectasis **reduces oxygenation** and **predisposes to infection.**

(Ref: Robbins/10th/675)

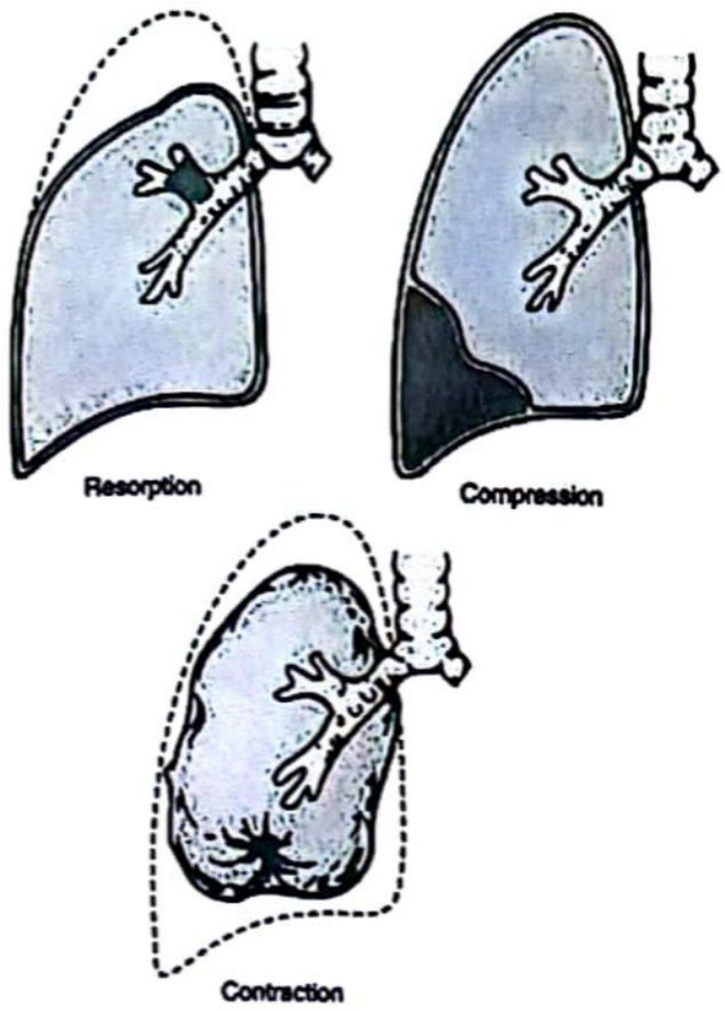


Fig: Various forms of acquired atelectasis. Dashed lines indicate normal lung volume.

Pulmonary Edema

Q. Define and classify pulmonary edema. What are the causes of pulmonary edema?

Ans.

Pulmonary edema: Pulmonary edema is the accumulation of **excessive interstitial fluid in the alveoli,** which can result from *hemodynamic disturbances* (cardiogenic pulmonary edema) or *increased capillary permeability* due to microvascular injury (non-cardiogenic pulmonary edema).

(Ref: Robbins/10th/675; BRS Pathology/5th/211)

Classification and causes of pulmonary edema:

1. **Haemodynamic edema:**
   - **i)** ***Increased hydrostatic pressure*** (increased pulmonary venous pressure)**:**
     - Left-sided heart failure (common)
     - Volume overload
     - Pulmonary vein obstruction
   - **ii)** ***Decreased oncotic pressure*** (less common)**:**
     - Hypoalbuminaemia
     - Nephrotic syndrome
     - Liver disease
     - Protein-losing enteropathies
   - **iii)** ***Lymphatic obstruction (rare)***
2. **Edema due to alveolar wall injury** (Microvascular or epithelial injury)**:**
   - **i)** ***Direct injury***
     - Infections: bacterial pneumonia
     - Inhaled gases: high concentration oxygen, smoke
     - Liquid aspiration: gastric contents, near-drowning
     - Radiation
     - Lung trauma

ii) ***Indirect injury***
- Systemic inflammatory response syndrome (e.g. associated with sepsis, burns, pancreatitis, extensive trauma)
- Blood transfusion–related
- Drugs and chemicals: chemotherapeutic agents (bleomycin), other medications (methadone, amphotericin B), heroin, cocaine, kerosene, paraquat

3. Edema of undetermined origin:
i) High altitude
ii) Neurogenic (central nervous system trauma).

(Ref: Robbins/10th/675)

Acute Lung Injury (ALI) & Acute Respiratory Distress Syndrome (ARDS)

Q. Define acute lung injury (ALI) & acute respiratory distress syndrome (ARDS).
Q. Short note: ARDS. (BUP-22Nv,20Nv/M,16Ju) ***(Important for VIVA)***
Ans.
Acute lung injury (ALI): Acute lung injury (ALI) is characterized by the abrupt onset of hypoxemia and bilateral pulmonary edema in the absence of cardiac failure (non-cardiogenic pulmonary edema).

(Ref: Robbins/10th/676)

ARDS: Acute respiratory distress syndrome (ARDS) is a **manifestation of severe ALI**.

(Ref: Robbins/10th/676)

Or,

ARDS is a clinical syndrome of **progressive respiratory insufficiency** caused by **diffuse alveolar damage** in the setting of sepsis, severe trauma, or diffuse pulmonary infection.

(Ref: Robbins/10th/678)

(***N.B***: Both ARDS and ALI are associated with inflammation-associated increases in pulmonary vascular permeability, edema, and epithelial cell death. The histologic manifestation of these diseases is ***diffuse alveolar damage***.)

Synonyms: "Shock lung", "diffuse alveolar damage", "acute alveolar injury", and "acute lung injury".

Conditions associated with development of ARDS:
1. **Infection:** Sepsis, diffuse pulmonary infections (Viral, *Mycoplasma,* and *Pneumocystis* pneumonia; miliary tuberculosis), gastric aspiration.
2. **Physical/injury:** Mechanical trauma including head injuries, pulmonary contusions, near-drowning, fractures with fat embolism, burns, ionizing radiation.
3. **Inhaled irritants:** Oxygen toxicity, smoke, irritant gases and chemicals.
4. **Chemical injury:** Heroin or methadone overdose, acetylsalicylic acid, barbiturate overdose, paraquat.
5. **Haematological conditions:** Transfusion associated lung injury (TRALI), disseminated intravascular coagulation (DIC).
6. **Others:** Pancreatitis, uraemia, cardiopulmonary bypass, hypersensitivity reactions (organic solvents, drugs).

(Ref: Robbins/10th/676)

Clinical features:
1. Profound dyspnea and tachypnea
2. Cyanosis and hypoxemia
3. Respiratory failure
4. Appearance of diffuse bilateral infiltrates on radiographic examination.

(Ref: Robbins/10th/678)

Obstructive Lung Diseases

Q. Define obstructive disease. Give example. ***(Very Important for VIVA)***
Q. What are the obstructive lung diseases? (SU-20M)
Q. What are the obstructive airway diseases? (CMU-22Nv)
Ans.
Obstructive lung diseases: Obstructive lung diseases are characterized by an **increase in resistance to airflow** due to **diffuse airway disease**, which may affect any level of the respiratory tract.

(Ref: Robbins/10th/678)

Or,

Obstructive lung diseases (or airway diseases) are characterized by an **increase in resistance to airflow** due to **partial or complete obstruction** at any level from the trachea and larger bronchi to the terminal and respiratory bronchioles.

(Ref: Robbins/9th/674)

An **FEV_1/FVC ratio** of **less than 0.7** generally indicates **obstructive disease**.

Common obstructive lung diseases include:

1. Chronic obstructive pulmonary disease (COPD)
   - Emphysema
   - Chronic bronchitis
2. Bronchial asthma
3. Bronchiectasis.

(Ref: Robbins/10th/678; BRS Pathology/5th/203)

(***N.B:*** **Emphysema** and **chronic bronchitis,** which are **often found together in the same patient,** almost certainly because they share the same major etiologic factor—cigarette smoking.)

(Ref: Robbins/10th/678)

Chronic Obstructive Pulmonary Disease (COPD)

Q. What do you mean by chronic obstructive lung diseases? (DU-18M)
Q. Define COPD. (CU-20Nv,18/17M,09/07Ja)
Q. Write briefly on COPD. (RMU-21M)
Q. Short note: COPD. (CU-13Ju) ***(Important for VIVA)***
Ans.
COPD (Chronic obstructive pulmonary disease): COPD is defined by the World Health Organization (WHO) as "a common, preventable and treatable disease that is characterized by **persistent respiratory symptoms** and **airflow limitation** that is due to **airway and/or alveolar abnormalities** caused by **exposure to noxious particles or gases.**"

It is currently the ***fourth leading cause of death*** in the world.

Characteristics include a marked decrease in the FEV_1 and an increased or normal forced vital capacity (FVC), resulting in a **decreased FEV_1 : FVC ratio**.

Clinicopathologic manifestations: COPD has two major clinicopathologic manifestations-

1. Emphysema
2. Chronic bronchitis.

Causes of COPD:

1. Cigarette smoking
2. Poor lung development early in life
3. Exposure to environmental and occupational pollutants
4. Airway hyperresponsiveness

5. Certain genetic polymorphisms (e.g. α_1-antitrypsin deficiency).

(**Note:** *Emphysema, chronic bronchitis, asthma, and bronchiectasis all are obstructive airway disease*).

(Ref: Robbins/10th/675; BRS Pathology/5th/202)

Emphysema

Necessary Lung Anatomy:

Pulmonary acinus: The part of the lung tissue **distal** to a **terminal bronchiole** is called an ***acinus.***

(***N.B*: *Lobule*** is a ***cluster of acini***.)

Parts of an acinus: An acinus consists of 3 parts:

1. ***Respiratory bronchioles*** originate from a terminal bronchiole.
2. Each respiratory bronchiole divides into several ***alveolar ducts***.
3. Each alveolar duct opens into many ***alveolar sacs (alveoli)*** which are blind ends of the respiratory passages.

(Ref: Robbins/10th/680; Harsh Mohan/7th/442)

Q. Define and classify emphysema. (CMU-23M,21Nv). ***(Important for VIVA)***

Q. Write the types of emphysema. (DU-18M)

Q. Discuss in brief the various types of emphysema. (SU-20M)

Ans.

Emphysema: Emphysema is a **chronic obstructive airway disease** characterized by **irreversible enlargement of airspaces distal to the terminal bronchiole,** accompanied by **destruction of their walls** without obvious fibrosis.

(Ref: Robbins/10th/675)

Or,

Emphysema is **dilation of air spaces** with **destruction of alveolar walls** and **lack of elastic recoil.**

(Ref: BRS Pathology/5th/204)

Types of emphysema: Emphysema is classified into four major types: (1) *centriacinar*, (2) *panacinar*, (3) *paraseptal*, and (4) *irregular.*

i) **Centriacinar (centrilobular) emphysema (95% of cases):** The central or proximal parts of the acini, formed by respiratory bronchioles are affected, whereas distal alveoli are spared. It occurs predominantly in ***heavy smokers***, often in association with chronic bronchitis (***smoking associated emphysema***).

ii) **Panacinar (panlobular) emphysema:** In this type the acini are uniformly enlarged from the level of the respiratory bronchiole to the terminal blind alveoli. This type of emphysema is associated with ***α_1-antitrypsin deficiency*** and is exacerbated by smoking.

iii) **Distal acinar (paraseptal) emphysema:** In this type, the proximal portion of the acinus is normal, but the distal part is predominantly involved. This type of emphysema probably underlies many of the cases of ***spontaneous pneumothorax*** in young adults.

iv) **Irregular emphysema (airspace enlargement with fibrosis):** In this type, the acinus is irregularly involved, is almost invariably associated with ***scarring***.

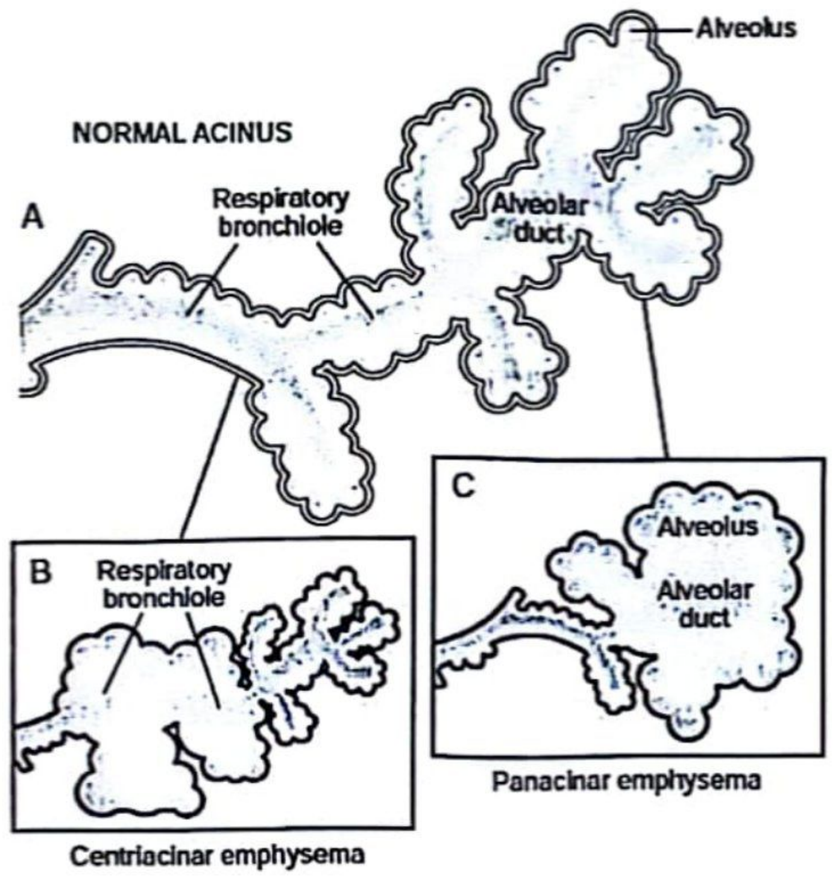


Fig: Emphysema.

(Ref: Robbins/10th/679)

Q. Give the etiopathogenesis of pulmonary emphysema. (DU-18M, CU-18M)

Ans.

Etiopathogenesis of emphysema: Clinically significant emphysema is largely confined to **smokers** and to patients with **α_1-antitrypsin deficiency**. Mechanisms relating to these factors that contribute to the development of emphysema include the following:

1. **Toxic injury and inflammation:** Inhaled **cigarette smoke** and other **noxious particles** damage respiratory epithelium and cause inflammation, which results in variable degrees of ***parenchymal destruction***. A wide variety of **inflammatory mediators** (including leukotriene B4, interleukin [IL]-8, TNF, and others) are released by **resident epithelial cells** and **macrophages** and variously attract inflammatory cells from the circulation (chemotactic factors), thus amplify the inflammatory process (proinflammatory cytokines), and **induce structural changes** (growth factors).
2. **Protease-antiprotease imbalance:** Several ***proteases*** are released from the inflammatory cells and epithelial cells that **break down connective tissue components**. In patients who develop emphysema, there is a relative deficiency of protective antiproteases (**congenital α_1-antitrypsin deficiency**).
3. **Oxidative stress:** Substances in tobacco smoke, alveolar damage, and inflammatory cells all produce **oxidants**, which may beget **tissue damage**, **endothelial dysfunction**, and **inflammation**.
4. **Infection:** Although infection is not thought to play an initiating role in the tissue destruction, **bacterial and/or viral infections** may acutely **exacerbate existing disease**.

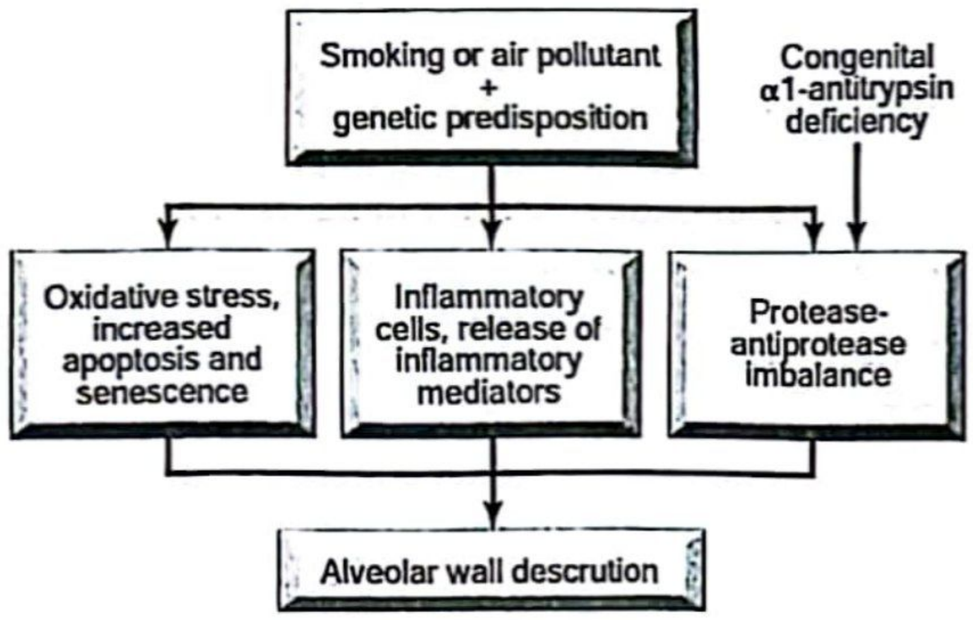


Fig: Pathogenesis of emphysema.

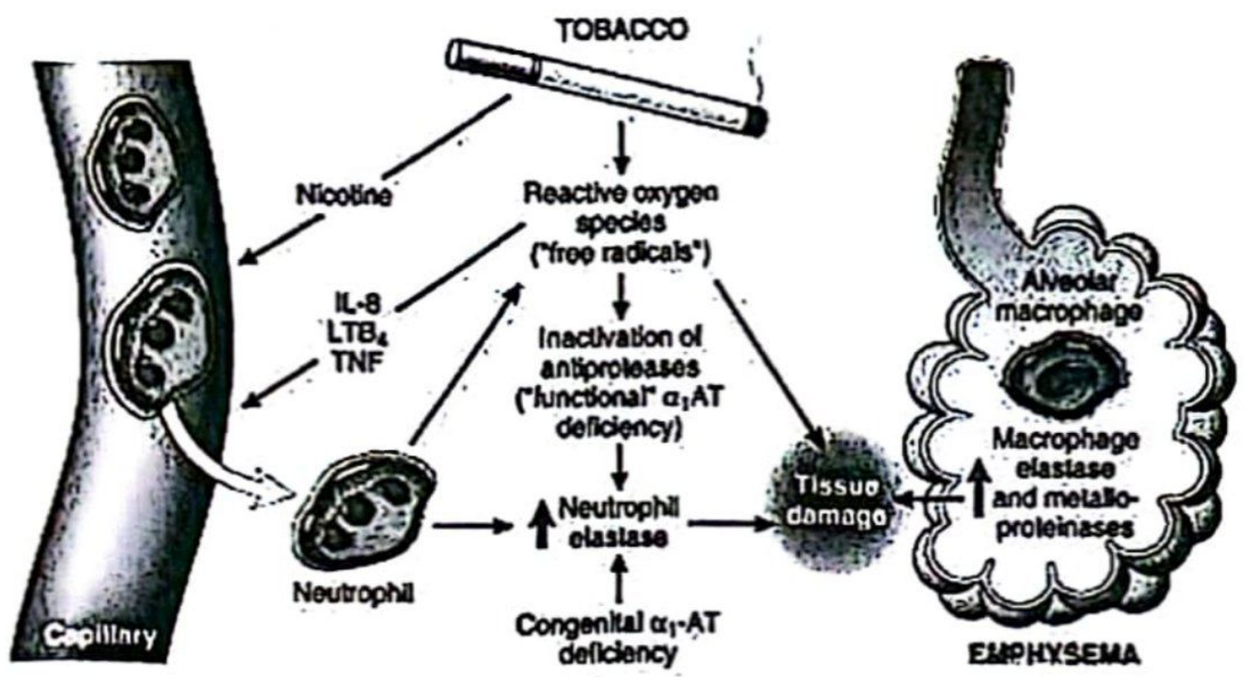


Fig: Pathogenesis of emphysema.

(Ref: Robbins/10th/680; Harsh Mohan/7th/460)

Protease-antiprotease hypothesis: α-1-antitrypsin (α-1-AT), also called **α-1-protease inhibitor** (α-1-Pi), is a **glycoprotein** that is normally synthesised in the **liver** and is distributed in the circulating **blood, tissue fluids** and **macrophages.**

The normal function of α-1-AT is to **inhibit** ***proteases*** and hence its name **α-1-protease inhibitor.** The ***proteases*** (mainly ***elastases***) are derived from **neutrophils.** Neutrophil elastase has the capability of digesting lung parenchyma but is inhibited from doing so by **anti-elastase effect of α-1-AT.**

The mechanism of **alveolar wall destruction** in emphysema by **elastolytic action** is based on the imbalance between **proteases** (chiefly ***elastase)*** and **anti-proteases** (chiefly ***antielastase):***

Th e α-1-AT deficiency develops in adults and causes pulmonary emphysema in smokers as well as in non-smokers, though smokers become symptomatic about 15 years earlier than non-smokers. The other organ showing effects of α-1-AT deficiency is the liver which may develop obstructive jaundice early in infancy, and cirrhosis and hepatoma (hepatocellular carcinoma) late in adulthood.

(Ref: Robbins/10th/680; Harsh Mohan/7th/460)

Q. Mention the clinical features and causes of death of emphysema.

Ans.

Clinical features of emphysema:

1. Dyspnea (with characteristic '**pursed lip breathing**')
2. Patient is quite distressed with obvious **use of accessory muscles of respiration**
3. Cough associated with **scanty mucoid sputum**

4. **Barrel-shaped, hyperresonant chest**
5. Weight loss
6. Expiratory airflow limitation (*best measured through spirometry, is the key to diagnosis*)
7. Patients are called '**pink puffers**' as they remain well oxygenated and have tachypnoea.
8. Cor pulmonale and eventually congestive heart failure *(related to secondary pulmonary vascular hypertension, and is associated with a poor prognosis).*

Causes of death of emphysema:

1. Respiratory acidosis and coma
2. Acute respiratory failure
3. Rupture of subpleural blebs leading to fatal pneumothorax.

(Ref: Robbins/10th/682; Harsh Mohan/7th/461)

Nice to Know:

Pulmonary bullae: *Advanced cases of emphysema show subpleural* ***bullae*** *which aree* ***air-filled cyst-like*** *or* ***bubble-like structures,*** *larger than 1 cm in diameter. They are formed by the* ***rupture of adjacent air spaces*** *and are the common cause of* ***spontaneous pneumothorax.***

(Ref: Harsh Mohan/7th/461)

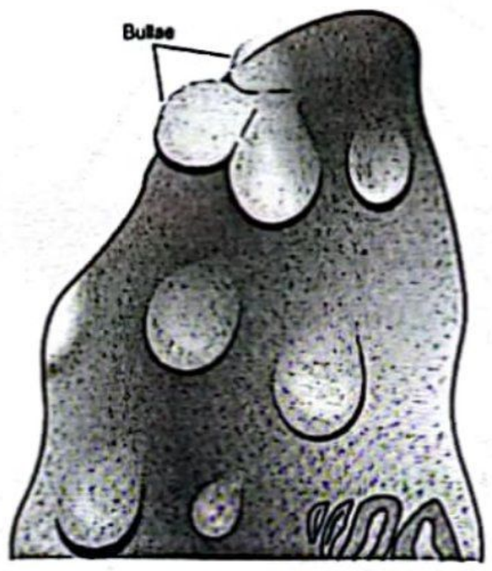


Fig: Bullous emphysema.

Chronic Bronchitis

Q. Define chronic bronchitis. ***(Very Important for VIVA)***
Q. Give the pathogenesis of chronic bronchitis. (CU-09Ja)
Ans.
Chronic bronchitis: Chronic bronchitis is defined clinically as **persistent cough with sputum production** for **at least 3 months** in at least **2 consecutive years** in the absence of any other identifiable cause.

Pathogenesis of chronic bronchitis:

Chronic irritation by inhaled substances such as **prolonged cigarette smoking** (90% of patients are smoker), **atmospheric pollutants** and **dusts** (from grain, cotton, and silica), **chemicals & fumes**

↓

Proteases released from neutrophils, such as *neutrophil elastase* and *cathepsin*, and *matrix metalloproteinases*

↓

Impairs ciliary movement
Inhibits the function of alveolar macrophages
Hypertrophy and hyperplasia of the mucus-secreting submucosal glands and goblet cells

↓

Hypersecretion of mucus in the airways

↓

Acute and chronic inflammatory responses involving neutrophils, lymphocytes,

and macrophages. Long-standing (chronic) inflammation associated with bronchiolar wall fibrosis

↓

Bronchial wall become thickened and oedematous

↓

Considerable **obstruction of airways** by mucus plugs with sputum overproduction

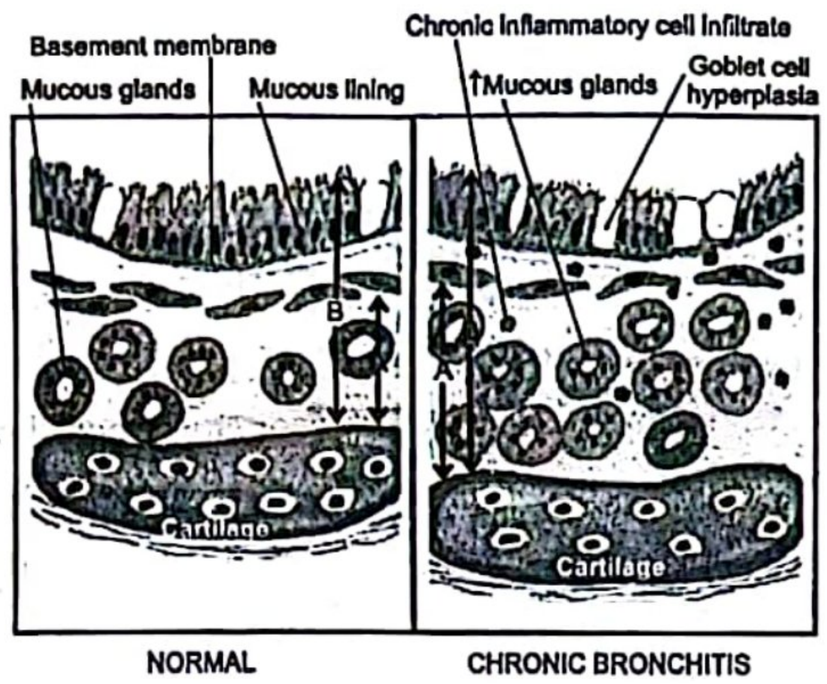
↓

Chronic bronchitis.

(Ref: Robbins/10th/680; Harsh Mohan/7th/459)

(***N.B:*** Bacterial, viral and mycoplasmal **infections** do not initiate chronic bronchitis, but usually occur **secondary to bronchitis.** They are important in triggering **acute exacerbation** of the disease).

(Ref: Robbins/10th/680; Harsh Mohan/7th/459)



Q. Name some important clinical features of chronic bronchitis.

Ans.

Clinical features of chronic bronchitis:

1. Persistent cough with copious sputum production (90% of patients are smoker)
2. Recurrent respiratory infections
3. Dyspnoea (mild; more on exertion)
4. Hypercapnia, hypoxemia, and mild cyanosis
5. Features of right heart failure (corpulmonale)
6. Patients are called '**blue bloaters**' due to cyanosis and oedema
7. Chest X-ray shows enlarged heart with prominent vessels.

(Ref: Robbins/10th/682; Harsh Mohan/7th/459)

(***N.B:*** Long-standing **chronic bronchitis** commonly leads to **pulmonary hypertension, cor pulmonale,** and **death** due to **heart failure.**)

(Ref: Robbins/10th/682)

Q. Compare and contrast between chronic bronchitis and emphysema. (V.V.I. for VIVA)

Ans.

Comparison between chronic bronchitis and emphysema:

Traits	Chronic bronchitis	Emphysema
1. Age	40-45 years	50-75 years
2. Dyspnea	Mild; late	Severe; early
3. Cough	Early; copious sputum	Late; scanty sputum
4. Secondary infection	Common	Occasional
5. Respiratory insufficiency	Early, periodic	End-stage
6. Cor pulmonale	Common	Uncommon, end-stage

7. Airway resistance	Increased	Normal or slightly increased
8. Disease location	Bronchus	Acinus
9. Pathogenesis	Impaired ciliary movement	Deficiency of α-1-antitrypsin
10. Major gross feature	Thickened bronchial wall	Distended air sacs
11. Main histology	Hypertrophy and hyperplasia of mucus-secreting glands	Destruction of alveolar walls
12. Elastic recoil	Normal	Low
13. Appearance	Blue bloater	Pink puffer
14. Chest radiograph	Prominent vessels; large heart size	Hyperinflation; small heart size

(Ref: Robbins/10th/682; Harsh Mohan/7th/459)

Q. Mention the treatment options of COPD. (For VIVA)

Ans.

Treatment options of COPD:

- Smoking cessation
- Oxygen therapy
- Long-acting bronchodilators with inhaled corticosteroids
- Antibiotics
- Physical therapy
- Bullectomy
- Lung volume reduction surgery and lung transplantation (in selected patients).

(Ref: Robbins/10th/682; Harsh Mohan/7th/461)

(***N.B***: Even with intervention, however, COPD often progresses and frequently proves fatal.)

(Ref: Robbins/10th/682)

Asthma

Q. Define and classify asthma.

Q. What are non-allergic causes of asthma?

Q. Short note: Bronchial asthma. *(Important for VIVA)*

Ans.

Asthma: Asthma is a heterogeneous disease, usually characterized by **chronic airway inflammation** and variable **expiratory airflow obstruction** that produces symptoms such as **wheezing, shortness of breath, chest tightness,** and **cough,** which vary over time and in intensity.

(Ref: Robbins/10th/683)

Or,

Asthma is characterized by **reversible bronchoconstriction** caused by **airway hyper-responsiveness** to a variety of stimuli.

(Ref: Robbins/10th/687)

Clinical features:

- Recurrent episodes of wheezing (in response to allergen exposure)
- Cough (particularly at night and/or in the early morning)
- Breathlessness
- Chest tightness.

(Ref: Robbins/10th/686)

Classification of asthma:

1. **Extrinsic** (allergic / atopic) **asthma** (evidence of allergen sensitization and immune activation): This **commonest type** of asthma is a classic example of **IgE-mediated (type-I) hypersensitivity reaction.** Disease begins in **childhood,** usually in patients with a **family history of allergy.**

2. **Intrinsic** (non-atopic) **asthma** (no evidence of allergen sensitization): It usually begins in **adult life** and is **not associated with a history of allergy**. It is several subtypes. In all types, episodes of bronchospasm may have diverse triggers, such as-

   - Respiratory infections (especially viral infections, e.g. rhinovirus, parainfluenza virus and respiratory syncytial virus etc.)
   - Irritants (e.g. smoke, fumes)
   - Cold air
   - Stress
   - Exercise
   - Drugs (e.g. aspirin and other non-steroidal anti-inflammatory drugs).

   (Ref: Robbins/10th/683; BRS Pathology/5th/203; Harsh Mohan/7th/464; Pathoma Lecture Notes)

Q. Write the differences between extrinsic (atopic) and intrinsic (non-atopic) asthma. ***(Important for VIVA)***

Ans.

Differences between between extrinsic and intrinsic asthma:

	FEATURE	EXTRINSIC ASTHMA	INTRINSIC ASTHMA
1.	*Age at onset*	In childhood	In adult
2.	*Personal/family history*	Commonly present	Absent
3.	*Preceding allergic illness (atopy)*	Present (e.g. rhinitis, urticaria, eczema)	Absent
4.	*Allergens*	Present (dust, pollens, danders etc)	None
5.	*Drug hypersensitivity*	None	Present (usually to aspirin)
6.	*Serum IgE level*	Elevated	Normal
7.	*Associated chronic bronchitis, nasal polyps*	Absent	Present
8.	*Emphysema*	Unusual	Common

(Ref: Harsh Mohan/7th/464)

Q. Mention the pathogenesis of bronchial asthma. (CU-19M)

Q. Short note: Atopic asthma. ***(For VIVA)***

Ans.

Atopic asthma: This is the **most common type of asthma** and is a classic example of **IgE-mediated (type-I) hypersensitivity reaction**. The disease usually begins in **childhood** and is triggered by **environmental allergens**, such as dusts, pollens, cockroach or animal dander (excreta), and foods etc.

Most patients of this type have a **positive family history of asthma** and/or **preceding allergic diseases** such as rhinitis, urticaria or infantile eczema etc.

Pathogenesis: Atopic asthma is caused by **IgE-mediated (type-I) hypersensitivity reaction** to environmental allergens in genetically predisposed individuals which includes an **early-phase** (immediate hypersensitivity) reaction and the **late-phase** reaction.

Initial sensitization to inhaled antigens
(e.g. house dust, pollens, animal danders, moulds etc.)
↓
Stimulate induction of T_H2 cells that release cytokines such as IL-4 & IL-5
↓
Cytokines promote IgE production by B cells, growth of mast cells (IL-4), and growth & activation of eosinophil (IL-5)
↓
Subsequent IgE mediated reaction to inhaled allergens elicits an **acute response** and a **late phase reaction**
↓

Exposure of pre-sensitized IgE coated must cells to the same or a cross-reacting Ag stimulates cross linking of IgE and the release of chemical mediators

↓

Direct stimulation of subepithelial vagal (parasympathetic) receptors provokes **bronchoconstriction** within minutes after stimulation and is called the **acute**, or **immediate response** (which consists of ***bronchoconstriction***, ***edema***, ***mucus hypersecretion***, and in extreme instances ***hypotension***)

↓

Mast cells on degranulation release cytokines (like histamine, leukotrienes, prostaglandins, platelet activating factor and chemotactic factors for eosinophils and neutrophils)

Net effects of these mediators are ***bronchoconstriction***, ***oedema***, ***mucus hypersecretion*** and ***accumulation of other leukocytes***, including neutrophils and particularly eosinophils (which is activated by IL-5)

↓

These **inflammatory cells** (notably **eosinophils, neutrophils**) set the stage for the **late-phase reaction,** which starts 4 to 8 hours later and may persist for 12 to 24 hours or more.

(Ref: Robbins/10th/684; Harsh Mohan/7th/464)

Nice to Know:

Phases of atopic asthma:

- **Early-phase** (immediate hypersensitivity) **reaction** is initiated by **IgE-sensitised mast cells** (tissue counterparts of circulating basophils) on the mucosal surface. **Mast cells on degranulation** release mediators like histamine, leukotrienes, prostaglandins, platelet activating factor and chemotactic factors for eosinophils and neutrophils. The net effects of these mediators are bronchoconstriction, increased mucus production, variable degrees of vasodilation, and increased vascular permeability.
- **Late phase reaction** follows the acute immediate response and is responsible for the **prolonged manifestations of asthma**. It is caused by excessive mobilisation of blood leucocytes that include ***neutrophils***, ***eosinophils***, and ***basophils***; ***lymphocytes*** and ***monocytes***. These result in further release of mediators which accentuate the above-mentioned effects. In addition, inflammatory injury is caused by **neutrophils** and by ***major basic protein (MBP) & eosinophil cationic protein*** of **eosinophils**.

(Ref: Robbins/10th/684; Harsh Mohan/7th/464)

Role of mediators produced by leukocytes and epithelial cells in the asthmatic response:

A. Mediators with major role in bronchospasm:

- **Leukotrienes C4, D4, and E4:** Cause prolonged ***bronchoconstriction*** as well as ***increased vascular permeability*** (edema) and ***increased mucus secretion.***
- **Acetylcholine** (released from intrapulmonary parasympathetic nerves)**:** Cause ***airway smooth muscle constriction*** by directly stimulating muscarinic receptors.
- **IL-5:** Associated with peripheral blood eosinophilia.
- **Galectin-10 (GAL10):** Released from eosinophils and forms crystals known as ***Charcot-Leyden crystals***. Recent studies have shown that these crystals are strong inducers of inflammation and mucus production.

B. Mediators with relatively minor role in bronchospasm:

- **Histamine:** Bronchoconstriction.
- **Prostaglandin D_2:** Bronchoconstriction and vasodilatation (increased vascular permeability → edema).
- **Platelet-activating factor:** Causes aggregation of platelets and release of serotonin from their granules.

C. Others (whose role has been insufficiently studied): IL-4, IL-13, TNF, chemokines (e.g. eotaxin, also known as CCL11), neuropeptides, nitric oxide, bradykinin, and endothelins.

(Ref: Robbins/10th/684)

Q Mention the histologic findings of asthma.
Q What is airway remodeling?
Ans.
Histologic findings of asthma:

1. Occlusion of bronchi and bronchioles by thick, tenacious mucus plugs, which often contain shed epithelium.
2. **Curschmann spirals,** which may result from extrusion of mucus plugs from subepithelial mucous gland ducts or bronchioles.
3. **Charcot-Leyden crystals** composed of the eosinophil-derived protein galectin-10
4. Other characteristic histologic findings of asthma, collectively called "***airway remodeling***", include:
   - Thickening of airway wall
   - Sub-basement membrane fibrosis (due to deposition of type-I and type-III collagens)
   - Increased vascularity
   - Increase in the size of the submucosal glands and number of airway goblet cells
   - Hypertrophy and/or hyperplasia of the bronchial wall muscle with increased extracellular matrix.

(Ref: Robbins/10th/686)

Bronchiectasis

Q. Define bronchiectasis. Enumerate the causes of bronchiectasis. ***(Important for VIVA)***
Q. Write briefly the aetio-pathology of bronchiectasis. (DU-05M)
Ans.
Bronchiectasis: Bronchiectasis is a disorder in which **destruction of smooth muscle and elastic tissue** by **inflammation** stemming from **persistent or severe infections** leads to ***permanent dilation of bronchi and bronchioles***.

(Ref: Robbins/10th/687)

Or,
Bronchiectasis is defined as **abnormal** and **irreversible dilatation** of the **bronchi and bronchioles** caused by **chronic infection,** with **inflammation** and **necrosis of the *bronchial wall*.**

(Ref: BRS Pathology/5th/205; Harsh Mohan/7th/465; Davidson's/23rd/578)

Causes / etiology of bronchiectasis:

A) Congenital or hereditary conditions that predispose to chronic infections:

1. Cystic fibrosis (CF)
2. Intralobar sequestration of the lung
3. Immunodeficiency states
4. Ciliary dysfunction syndromes
   - Primary ciliary dyskinesia (immotile cilia syndrome)
   - Kartagener's syndromes (bronchiectasis, situs inversus and sinusitis)

B) Acquired:

1. **Post-infectious conditions:** Severe necrotizing pneumonia caused by **bacteria** (*M. tuberculosis, S. aureus*, H. *influenzae*, Pseudomonas) **viruses** (adenovirus, influenza virus, HIV), and **fungi** (Aspergillus species) may develop bronchiectasis as a complication.
2. **Bronchial obstruction:** Due to tumours, enlarged lymph nodes, foreign bodies, or mucus impaction.
3. **Immune disorders:** Rheumatoid arthritis, SLE, inflammatory bowel disease (IBD), and post-transplantation (chronic rejection after lung transplant and chronic graft-versus-host disease after hematopoietic stem cell transplantation).
4. **Idiopathic** (up to 50% of cases).

(Ref: Robbins/10th/687)

Pathogenesis: ***Loss of muco-ciliary clearance system*** is the main problem. **Mucus accumulation followed by bacterial overgrowth** leads to **pus filled infection** and **permanent dilation of airways.**

Bronchial obstruction (e.g. by mucus impaction, tumours, or foreign bodies)
↓
Normal clearing mechanisms are impaired
↓
Pooling of secretions distal to the obstruction
↓
Infections
↓
Inflammation of the airway associated with necrosis & fibrosis
↓
Eventual permanent dilatation of the airways.

(Ref: Robbins/10th/687; Davidson's/23rd/578; Harsh Mohan/7th/465; Pathoma Lecture Notes)

Nice to Know:

Relation of bronchiectasis with cystic fibrosis (CF): *In cystic fibrosis, the* ***viscid mucous secretions from*** *all the exocrine glands of the body, including the sub mucosal glands of the respiratory tract cause* ***obstruction, dilatation*** *and* ***infection*** *of the airways.*

(Ref: Harsh Mohan/7th/631)

Q. What is Kartagener's syndrome? *(For VIVA)*

Ans.

Kartagener's syndrome: Kartagener's syndrome is a **ciliary dysfunction syndrome** manifested by **sinusitis, bronchiectasis,** and **situs inversus** (sometimes with **hearing loss** and **male sterility**).

Cause: It is caused by a **defect** in the motility of **respiratory, auditory,** and **sperm cilia** that is referred to as **primary ciliary dyskinesia,** an uncommon ***autosomal recessive syndrome.*** In this condition, there is a **structural defect in dynein arms of cilia.**

Pathogenesis: Impaired ciliary activity predisposes to ***infection in the sinuses*** and ***bronchi*** and ***disturbs embryogenesis***, sometimes resulting in ***situs inversus***. **Male infertility** is an important manifestation of *ciliary dyskinesia.*

(Ref: Robbins/10th/687; Davidson's/23rd/550,578; BRS Pathology/5th/205; Pathoma Lecture Notes)

Q. What is presentation and complication of bronchiectasis? *(For VIVA)*

Ans.

Presentation of bronchiectasis:

- Severe, persistent cough
- Expectoration of foul smelling, sometimes bloody sputum
- Dyspnea and orthopnea (in severe cases)
- Pleuritic chest pain
- Hemoptysis (which may be massive)
- Recurrent pneumonia

Complication of bronchiectasis:

- Development of clubbing of the fingers
- Metastatic brain abscess
- Amyloidosis
- Corpulmonale.

(Ref: Robbins/10th/688; Davidson's/23rd/578; BRS Pathology/5th/205; Pathoma Lecture Notes)

Nice to Know: V.V.I. for Conception

Morphologic features: Bronchiectasis usually affects the lower lobes **bilaterally,** particularly **distal bronchi** and **bronchioles** beyond the segmental bronchi. The airways are **dilated,** sometimes **up to four times** normal size.

Grossly, the lungs may be involved **diffusely** or **segmentally** (locally). **Bilateral** involvement of **lower lobes** occurs most frequently.

The **dilated airways**, depending upon their gross or broncho-graphic appearance, have been **subclassified** into the following different types:

1. ***Cylindrical:*** The most common type characterised by **tube-like** bronchial dilatation.
2. ***Fusiform:*** Having **spindle-shaped** bronchial dilatation.
3. ***Saccular:*** Having **rounded sac-like** bronchial distension.
4. ***Varicose:*** Having **irregular** bronchial enlargements.

Cut surface of the affected lobes, generally the lower zones, shows characteristic **honey-combed** appearance.

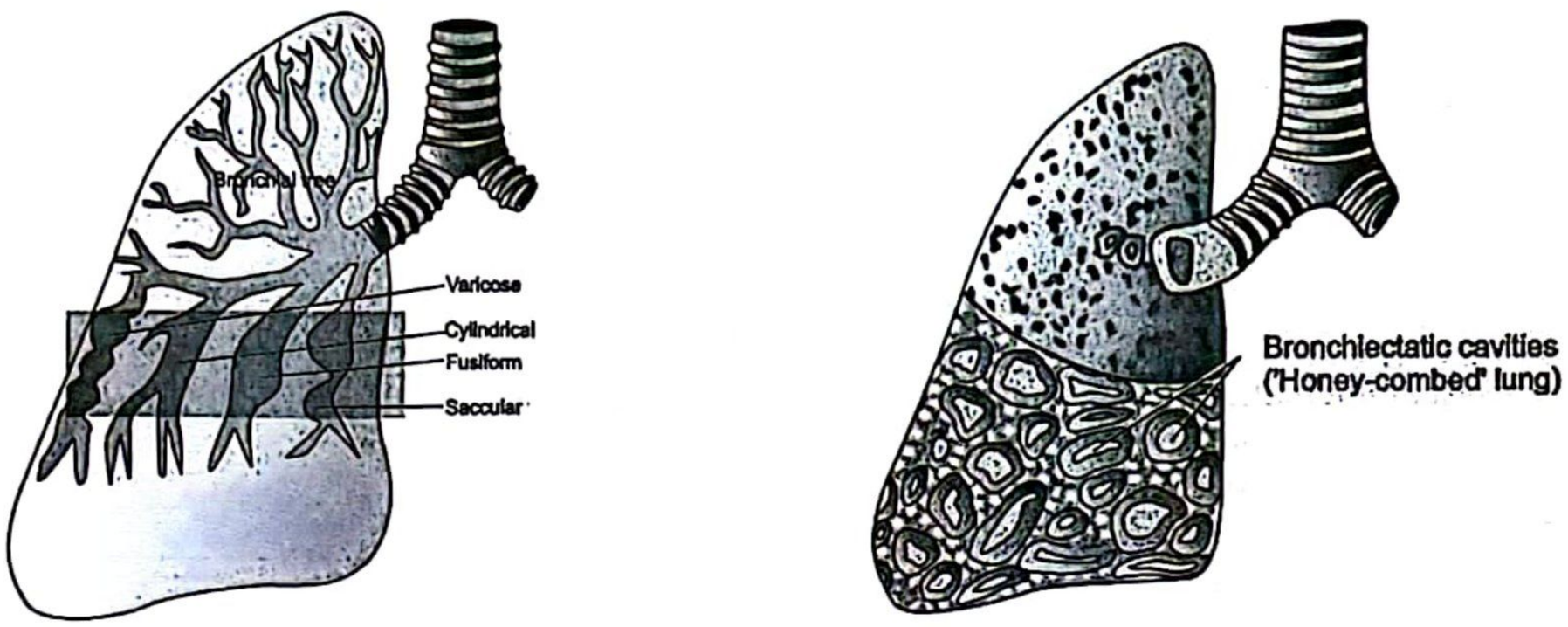


Fig: ***(Left)*** **Types of bronchial dilatations in bronchiectasis;** ***(Right)*** **Sectioned surface shows honey-combed appearance of the bronchiectatic lung in the lower lobe.**

(Ref: Robbins/10th/687; Harsh Mohan/7th/465)

Restrictive Lung Diseases

Q. What do you mean by restrictive lung disease? (DU-18M) **Give example.**

Ans.

Restrictive lung disease: Restrictive lung diseases are a group of disorders characterized by **reduced expansion of lung parenchyma** and **decreased total lung capacity.**

(Ref: Robbins/10th/678; BRS Pathology/5th/203)

In restrictive lung disease, both total lung capacity and FEV1 decrease proportionately, resulting in a **normal FEV_1/FVC ratio.**

Restrictive defects occur in two broad kinds of conditions:

1. **Chest wall disorders** (e.g. severe obesity, pleural diseases, kyphoscoliosis and neuromuscular diseases such as poliomyelitis)
2. **Chronic interstitial and infiltrative diseases,** such as pneumoconioses and interstitial fibrosis.

(Ref: Robbins/10th/678; BRS Pathology/5th/203)

Patients have dyspnea, tachypnea, end-inspiratory crackles, and eventual cyanosis, without wheezing or other evidence of airway obstruction. The **classic functional abnormalities** are reductions in diffusion capacity, lung volume, and lung compliance. **Chest radiographs** show bilateral lesions that take the form of small nodules, irregular lines, or ***ground-glass shadows,*** all corresponding to areas of interstitial fibrosis. Although the entities can often be distinguished in their early stages, advanced forms are hard to differentiate because all result in diffuse scarring of the lung, often referred to as ***end-stage lung*** or ***honeycomb lung***. Eventually, secondary pulmonary hypertension and right sided heart failure (cor pulmonale) may result.

(Ref: Robbins/10th/688)

Interstitial Lung Diseases

Interstitial lung diseases: Chronic interstitial pulmonary diseases are a heterogeneous group of disorders characterized predominantly by **inflammation and fibrosis of the lung interstitium** associated with pulmonary function studies indicative of restrictive lung disease.

(Ref: Robbins/10th/688)

Or,

Interstitial lung disease is a heterogeneous group of disorders characterized by **interstitial accumulations of cells or noncellular material** within the alveolar walls that restrict expansion and often interfere with gaseous exchange.

(Ref: BRS Pathology/5th/205)

Major categories of chronic interstitial lung diseases:

1. **Fibrosing**
   - Usual interstitial pneumonia (idiopathic pulmonary fibrosis)
   - Nonspecific interstitial pneumonia
   - Cryptogenic organizing pneumonia
   - Connective tissue disease-associated
   - Pneumoconiosis
   - Drug reactions
   - Radiation pneumonitis
2. **Granulomatous**
   - Sarcoidosis
   - Hypersensitivity pneumonitis
3. **Eosinophilic**
4. **Smoking-related**
   - Desquamative interstitial pneumonia
   - Respiratory bronchiolitis-associated interstitial lung disease
5. **Others**
   - Langerhans cell histiocytosis
   - Pulmonary alveolar proteinosis
   - Lymphoid interstitial pneumonia.

(Ref: Robbins/10th/688)

Pneumoconiosis: ***(Very Important for VIVA)*** The term *pneumoconiosis* describes the non-neoplastic lung reaction to inhalation of mineral dusts encountered in the workplace, including disease induced by chemical fumes and vapors.

(Ref: Robbins/10th/691)

Or,

Pneumoconioses encompass a group of chronic fibrosing diseases of the lung resulting from exposure to organic and inorganic particulates, most commonly mineral dust.

(Ref: Robbins/10th/695)

Lung diseases caused by air pollutants:

Agent	Disease (type of pneumoconiosis)
Mineral dusts:	
Coal dust	Anthracosis
Silica	Silicosis
Asbestos	Asbestosis Pleural plaques Caplan syndrome Mesothelioma Carcinoma of the lung, larynx, stomach, colon
Beryllium	Acute berylliosis Beryllium granulomatosis Lung carcinoma (?)
Iron oxide	Siderosis
Organic dusts that induce hypersensitivity pneumonitis	
Moldy hay	Farmer's lung
Bagasse	Bagassosis
Organic dusts that induce asthma	
Cotton, flax, hemp	Byssinosis
Red cedar dust	Asthma
Chemical fumes and vapors	
Nitrous oxide, sulfur dioxide, ammonia, benzene, insecticides	Bronchitis, asthma Pulmonary oedema ARDS Mucosal injury Fulminant poisoning

(Ref: Robbins/10th/692)

Pulmonary Embolism and Infarction

It is the major cause of **sudden death in hospitalized (bedridden) patients.** Occlusion of the pulmonary artery is nearly embolic and main source is thrombi in the deep veins of the leg (e.g. politeal vein) in more than 95% of cases.

Morphology:

Macroscopic: The pulmonary infarct is classically hemorrhagic and appears as a raised, red-blue area in the early stages.

Histologically: The diagnostic feature of acute pulmonary infarction is the ischemic necrosis of the lung substance within the area of hemorrhage, affecting the alveolar walls, bronchioles, and vessels.

Clinical features:

- Large pulmonary embolus impacted in the main pulmonary artery causing **instantaneous death.**
- Small emboli induce only **transient chest pain, cough,** and **pulmonary hemorrhage.**

Laboratory diagnosis:

- Serum D-dimer measurement
- Ventilation perfusion (V/Q) scanning
- Chest x-ray: May be normal; or a wedge-shaped pulmonary infiltrate (usually after 12 to 36 hours)
- CT pulmonary angiography (definitive diagnosis)

Complication:

- Pulmonary hypertension
- Pulmonary vascular sclerosis
- Chronic corpulmonale.

(Ref: Robbins/10th/702)

Pulmonary Infections

Important and common examples of acute and chronic pulmonary infections are:

1. ***Acute pulmonary infections*:**
   - Acute upper respiratory tract infections caused by viruses (common cold, pharyngitis)
   - Pneumonias (bacterial, viral, mycoplasmal, and fungal)
   - Fungal infections
   - Lung abscess

2. ***Chronic pulmonary infections*:**
   - Pulmonary tuberculosis.

(Ref: Robbins/10th/705; Harsh Mohan/7th/448)

Pneumonia

Q. Define (DU-19M,17Nv, RMU-22/21M,20/19/18/17M,16Ja, SU-20Nv, CU-14Ja) **& classify pneumonia.** (DU-21Oct/M,10Ju,06S/Ja, RMU-23/22/21M,20/19/18M,14/12Ja,09Ju, SU-22Nv/M, 20Nv,18M,12/11/09Ja,09Ju,06Ja, CU-11/08/05/04Ja)
Q. Write the causes of pneumonia. (RU-16Ja)
Q. Name the etiologic agents of pneumonia. (DU-19M)
Ans.
Pneumonia: Any ***infection of the lung parenchyma*** is called pneumonia.

(Ref: Robbins/10th/705)

Or,

Pneumonia is an **inflammatory process** of infectious origin affecting the **pulmonary parenchyma.**

(Ref: BRS Pathology/5th/211)

Or,

Pneumonia is defined as **acute inflammation** of the **lung parenchyma distal to the terminal bronchioles** (consisting of the respiratory bronchiole, alveolar ducts, alveolar sacs and alveoli).

(Ref: Harsh Mohan/7th/448)

(***N.B:*** The terms **'pneumonia'** and **'pneu monitis'** are often used **synonymously for inflammation of the lungs**, while **'consolidation'** (meaning **solidification**) is the term used for **gross and radiologic appearance** of the **lungs in pneumonia.**)

Classification of pneumonia:

A) According to anatomical distribution (morphological classification):
1. Lobar pneumonia
2. Broncho-pneumonia

B) According to etiological agents (causes of pneumonia):
1. **Bacterial (most common):** *Streptococcus pneumoniae, H. influenzae, Klebsiela pneumoniae, Staphylococcus aureus, Mycoplasma pneumoniae, Legionella pneumophila, Chlamydia pneumoniae, Chlamydia psittaci, Pseudomonas aeruginosa, Micobacterium tuberculosis, Moraxella catarrhalis.*
2. **Viral:** Influenza, parainfluenza, measles, respiratory syncytial virus, corona virus, cytomegalovirus, mumps virus, rhinovirus, adenovirus, rubeola, and varicella viruses.

3. **Fungal:** Candida, actinomycosis, histoplasma.
4. **Protozoal:** *Entamoeba histolytica*, *Toxoplasma gondii*, *Pneumocystis carinii*.
5. **Mycoplasmal:** *Mycoplasma pneumoniae*.
6. **Chlamydial:** *Chlamydia pneumoniae*.
7. **Rickettsial:** Typhus & Q-fever (*Coxiella burnetti*).

C) **<u>According to nature of host reaction</u>:**

1. Fibrinous
2. Suppurative
3. Serofibrinous.

(Ref: Robbins/10th/705)

Q. Classify pneumonia syndrome. (For VIVA)

Ans.

<u>Classification of pneumonia syndrome</u>:

1. **Community acquired acute pneumonia (CAP): *(Important for VIVA)***
   - *Streptococcus pneumoniae*
   - *H. influenzae*
   - *Staphylococcus aureus*
   - *Mycoplasma pneumoniae*
   - *Chlamydia pneumoniae*
   - *Legionella pneumophila*
   - *Moraxella catarrhalis*
   - Enterobacteriaceae *(Klebsiella pneumoniae)* and *Pseudomonas* spp.
   - *Chlamydia* spp. *(C. pneumoniae, C. psittaci, C. trachomatis)*
   - *Coxiella burnetii* (Q fever)
   - ***Viruses:*** Respiratory syncytial virus, influenza A and B, parainfluenza virus, measles virus, adenovirus, corona virus, human metapneumovirus (children) etc. ***(Important for VIVA)***
2. **Health care-associated pneumonia:**
   - *Staphylococcus aureus* (methicillin-sensitive)
   - *Staphylococcus aureus* (methicillin-resistant)
   - *Pseudomonas aeruginosa*
   - *Streptococcus pneumoniae*
3. **Nosocomial or hospital-acquired pneumonia:** Nosocomial or ***hospital-acquired pneumonias*** are defined as ***pulmonary infections acquired in the course of a hospital stay.*** ***(Important for VIVA)***
   - Gram-negative rods
   - Enterobacteriaceae (*Klebsiella* spp., *E. coli*)
   - *Pseudomonas* spp.
   - *Staphylococcus aureus* (usually penicillin resistant).
4. **Aspiration pneumonia:** Anaerobic oral flora (*Bacteroides*, *Prevotella*, *Fusobacterium*, *Peptostreptococcus*), admixed with aerobic bacteria (*Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*)
5. **Chronic pneumonia:**
   - *Nocardia*
   - *Actinomyces*
   - Granulomatous: *Mycobacterium tuberculosis* and atypical mycobacteria, *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*
6. **Necrotizing pneumonia and lung abscess:** The term **'pulmonary abscess'** describes a ***local suppurative process*** within the lung, characterized by necrosis of lung tissue.

- Anaerobic bacteria *(extremely common)*, with or without mixed aerobic infection
- *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pyogenes*, and type 3 pneumococcus (uncommon)

7. **Pneumonia in the immuno-compromised host:**
   - Cytomegalovirus
   - *Pneumocystis jiroveci*
   - *Mycobacterium avium-intracellulare* complex
   - Invasive aspergillosis
   - Invasive candidiasis
   - "Usual" bacterial, viral, and fungal organisms *(listed above)*.

(Ref: Robbins/10th/706)

Nice to Know:

Community acquired acute pneumonia (CAP): Community-acquired acute pneumonia (CAP) refers to **lung infection** in otherwise healthy individuals that is **acquired from the normal environment** (in contrast to hospital acquired pneumonia). It may be **bacterial** or **viral**. Often, the bacterial infection follows an upper respiratory tract viral infection. Bacterial invasion of the **lung parenchyma** causes the alveoli to be filled with an **inflammatory exudate**, thus causing **consolidation ("solidification")** of the pulmonary tissue. Many variables, such as the specific etiologic agent, the host reaction, and the extent of involvement, determine the precise form of pneumonia.

Predisposing conditions include-

- Extremes of age
- Chronic diseases (congestive heart failure, COPD, and diabetes)
- Congenital or acquired immune deficiencies
- Decreased or absent splenic function (sickle cell disease or post-splenectomy, which puts the patient at risk for infection with encapsulated bacteria such as pneumococcus).

Streptococcus pneumoniae* (*pneumococcus*)** is the ***most common cause of **community-acquired pneumonia (CAP)**. ***(Important for VIVA)***

(Ref: Robbins/10th/706)

Aspiration pneumonia: It occurs in markedly debilitated patients or those who aspirate gastric contents either while unconscious (e.g., after a stroke) or during repeated vomiting.

(Ref: Robbins/10th/711)

V.V.I for VIVA

Organisms causing typical pneumonia:

- *Streptococcus pneumoniae*
- *H. influenzae*
- *Klebsiela pneumoniae*
- *Staphylococcus aureus*

Organisms causing atypical pneumonia:

- *Mycoplasma pneumoniae*
- *Legionella pneumophila*
- *Chlamydia pneumoniae*
- *Chlamydia psittaci*
- *Coxiella burnetii* (Q fever)
- Actinomyces israelii
- Viruses.

Nice to Know:

The microorganisms gain entry into the lungs by one of the following four routes:

1. ***Inhalation*** of the microbes present in the air.
2. ***Aspiration*** of organisms from the nasopharynx or oropharynx.
3. ***Haematogenous spread*** from a distant focus of infection.
4. ***Direct spread*** from an adjoining site of infection.

(Ref: Harsh Mohan/7th/448)

Q. What is lobar pneumonia (SU-04S,03Ja) **and bronchopneumonia?**
Q. Discuss the etiology (DU-14Ja, RU-17M) **& pathogenesis of lobar** (DU-06Ja,CU-05Ja) **pneumonia.**
Q. Discuss the pathogenesis of bacterial pneumonia.
Ans.

Bacterial pneumonia: It has two patterns of anatomic distribution: ***lobar pneumonia*** and ***bronchopneumonia***.

1. **Lobar pneumonia:** It is an acute bacterial infection resulting in **fibrino-suppurative consolidation** of **a large portion of a lobe** or **of an entire lobe.** The ***lower lobes*** are affected ***most commonly***.

2. **Bronchopneumonia:** It is an acute bacterial infection characterized by **patchy consolidation of the lung** (3-4 cm. in diameter, more ***often multilobar***, often ***bilateral & basal***).

(Ref: Robbins/10th/704)

Pathogenesis / predisposing factors of bacterial pneumonia: Pneumonia can result whenever the ***local defense mechanisms are impaired*** or the ***systemic resistance of the host is lowered***.

A) Factors altering the defense mechanisms of lung:

1. ***Altered consciousness*:** Oropharyngeal contents may be ***aspirated*** in states causing unconsciousness e.g. in coma, cranial trauma, seizures, stroke, drug overdose, alcoholism etc.
2. ***Loss or suppression of cough reflex*:** It may allow ***aspiration of gastric contents***, as a result of coma, anaesthesia, neuromuscular disorders, drugs, or chest pain.
3. ***Dysfunction of the mucociliary apparatus*:** Passage of bacteria into the lung parenchyma is favoured by either ***impairment of ciliary function*** or ***destruction of ciliated epithelium***, owing to cigarette smoking, viral respiratory infections, inhalation of hot or corrosive gases, old age, or genetic defects of ciliary function (e.g. immotile cilia syndrome).
4. ***Accumulation of secretions*** in conditions such as cystic fibrosis and bronchial obstruction.
5. ***Interference with the phagocytic and bactericidal activities of alveolar macrophages*** by alcohol, tobacco smoke, anoxia, or oxygen intoxication.
6. ***Pulmonary congestion and edema.***

B) Factors lowering the resistance of the host:

1. Chronic diseases.
2. Immunologic deficiency
3. Treatment with immunosuppressive agents
4. Leukopenia.

(Ref: Robbins/10th/705; Harsh Mohan/7th/448)

Nice to Know:

***Bronchopneumonia** is particularly frequent at the extremes of life (i.e. in infancy and old age), as a terminal event in chronic debilitating diseases and as a secondary infection following viral respiratory infections such as influenza, measles etc.*

(Ref: Harsh Mohan/7th/452)

Q. Discuss the morphology of lobar pneumonia. (DU-06S/Ja,04Ja, SUST-21/19Nv,17M,16Ja, 14Ju,11Ja,09Ju, RU-20/17M,15/14Ja,09Ju, CU-08Ja)
Q. Enumerate morphologic stages of pneumonia. (RU-18M,16Ja)
Q. Give the morphology of different stages of lobar pneumonia. (SU-22Nv/M,20Nv,18M,15Ju, RMU-21M)
Q. Write the pathological changes / stages of lobar pneumonia. (CU-20M,11Ja, SU-13Ja)
Q. Name the classical stages of lobar pneumonia. (DU-10Ju, SU-06Ja, CU-04Ja)
Q. Name the stages of lobar pneumonia. (DU-21Oct/M, SU-12/09/06Ja)
Q. Briefly discuss the stages of lobar pneumonia. (DU-17Nv, CMU-21M,19Nv,14Ja)
Q. What are the stages of acute bacterial pneumonia? (DU-19M)
Ans.

Morphology / pathology of lobar pneumonia: ***(Very***Very Important for VIVA)***

Stages	Gross	Microscopic
1. Stage of congestion: INITIAL PHASE (1 - 2 days)	The involved lobe is ***heavy***, ***boggy***, ***red*** and subcrepitant	▪ Vascular engorgement ▪ Intra-alveolar fluid with few neutrophils ▪ Often presence of numerous bacteria in alveoli
2. Stage of red hepatization: EARLY CONSOLI DATION ($2 - 4^{th}$ day)	The affected lobe appears ***red***, ***firm*** and ***airless*** with ***liver-like consistency*** (so, called hepatization)	▪ Vascular engorgement, ***packed with RBC & WBC (neutrophil)*** ▪ The alveoli are filled with massive ***exudation*** with ***red cells***, ***WBC*** and ***fibrin*** (coagulated)
3. Stage of grey hepatization: LATE CONSOLI DATION ($4^{th} - 8^{th}$ day)	▪ The affected lobe appears ***greyish brown*** ▪ The cut surface is dry & firm, having ***liver-like consistency***	▪ ***Disintegrated red cells*** in alveoli (less RBC) ▪ Presence of ***fibrino-suppurative exudates*** ▪ ***Macrophages*** begin to appear in the exudate
4. Stage of resolution (8^{th} day)	Almost ***normal*** appearance	▪ The exudate within alveolar spaces undergo progressive ***enzymatic digestion***, produce a granular semifluid debris ▪ The debris is removed by ***resorption*** in ***lymphatics*** and ***ingestion by macrophage*** (***coughed up***)

(Ref: Robbins/10^{th}/708; Harsh Mohan/7^{th}/449)

(***N.B:*** The term **hepatisation** in pneumonia refers to **liver-like consistency** of the affected lobe on cut section.)

Q. Enumerate the clinical features & complications of pneumonia.
Q. Give the complications of pneumonia. (RU-18M,15Ja,10Ju, CU-14Ja)
Q. Enumerate the complications of lobar pneumonia. (DU-21Oct/M,06S, RMU-21/20/19M,14Ja, CU-04Ja)
Ans.

Clinical features of pneumonia: ***(Very***Very Important for VIVA)***

1. High fever
2. Shaking chills
3. Productive cough with mucopurulent/rusty sputum
4. Occasional hemoptysis
5. Pleuritic chest pain
6. Hypoxia with shortness of breath

7. Cyanosis (sometimes).

(Ref: Robbins/9th/705; BRS Pathology/5th/211; Pathoma Lecture Notes)

Complications of pneumonia: ***(Very***Very Important for VIVA)***

1. Organization / fibrosis
2. Para-pneumonic effusion
3. Empyema (encysted pus in the pleural cavity)
4. Lung abscess
5. Lobar collapse
6. Pneumothorax
7. Bacteremic dissemination to various organs, causing-
   - Bacterial endocarditis
   - Myocarditis
   - Purulent pericarditis
   - Meningitis
   - Brain abscess
   - Suppurative arthritis
   - Otitis media, mastoiditis
   - Renal failure
   - Multi-organ failure.

(Ref: Robbins/10th/708; Lecture DMC)

Q. Name the investigations done to diagnose a case of pneumonia. (DU-19M)

Ans.

Investigations for diagnosis of pneumonia:

1. Hb%, TC, DC, ESR:
   - In bacterial pneumonia: Polymorphonuclear leukocytosis.
   - In atypical pneumonia: Normal or slightly increased leukocytes.
   - In viral pneumonia: Leukopenia.
2. X-ray chest (P/A view): Homogenous opacity with air bronchogram (usually found after 12 to 18 hours).
3. Sputum: Gram staining, C/S (aerobic and anaerobic).
4. Blood C/S (positive in *pneumococcal pneumonia*).
5. Arterial blood gas analysis.
6. Others (according to etiology):
   - Pneumococcal antigen in serum.
   - Mycoplasma antibody detection (agglutination, CFT), Coomb's test, C/S in special media
   - Antibody against virus, chlamydia, legionella
   - Urinary legionella pneumophila antigen
   - CRP (high).

(Ref: Lecture DMC & SSMC)

Q. Mention the differences between lobar and bronchopneumonia. (DU-17Nv,10Ju)

Q. Mention the differences between lobar and lobular pneumonia. (RMU-23M,22Nv)

Q. Short note: Bronchopneumonia. (SU-10Ju)

Q. Short note: Lobar pneumonia. (DU-15Ju, BUP-22M)

Ans.

Differences between lobar and bronchopneumonia:

Traits	Lobar pneumonia	Bronchopneumonia
1. Definition	It is an acute bacterial infection resulting in **fibrino-suppurative consolidation** of a **large portion of a lobe** or of **an entire lobe**	It is an acute bacterial **infection** characterized by **patchy consolidation** of the lung *(3-4 cm. in diameter, more often **multilobar**, often **bilateral & basal**)*
2. Common etiologic agents	*Streptococcus pneumoniae* (90 - 95% of cases)	No definite micro-organisms (low virulent micro-organisms are responsible e.g. staphylococci, streptococci, *pseudomonas*, *haemophilus influenzae* etc.)
3. Predisposing factors	More often affects healthy individuals	Pre-existing diseases, e.g. chronic debility, terminal illness, flu, measles
4. Age group	More common in young adults	Extremes of age (infants and old age)
5. X-ray findings	Consolidation	Mottled focal opacities
6. Nature of consolidation	Fibrino-suppurative consolidation	Patchy consolidation
7. Distribution of consolidation	Affects large portion of a lobe or of an entire lobe, and usually unilateral	Affects several lobes of the lung and often bilateral
8. Fall of temperature	Sudden drop of temperature	Gradual fall of temperature
9. Prognosis	Better response to treatment, resolution common, prognosis good	Response to treatment variable, organisation may occur, prognosis poor
10. Complications	Less common; pleural eff usion, empyema, lung abscess, organization	Bronchiectasis may occur; other complications same as for lobar pneumonia
11. Mode of death	Due to septicaemia	Related or associated disease

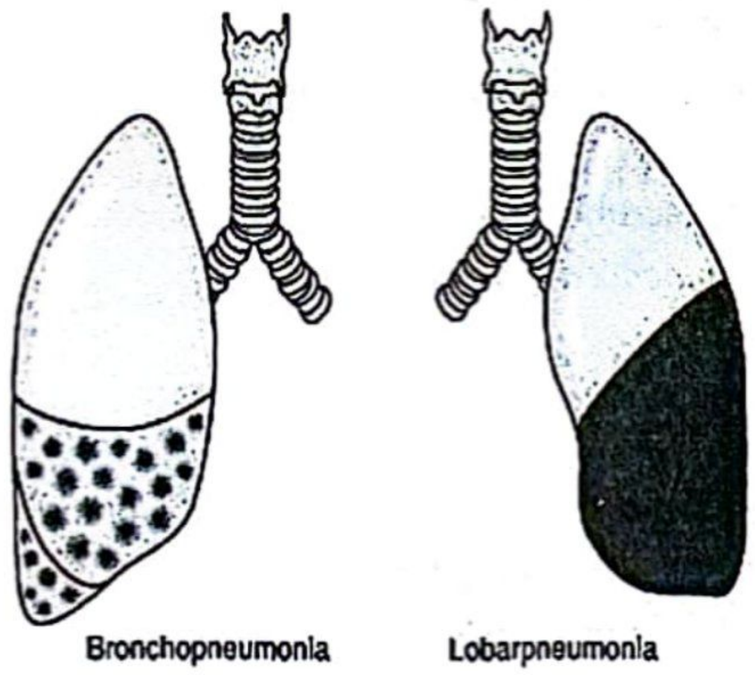


Fig: Lobar & bronchopneumonia.

(Ref: Robbins/10th/707; Harsh Mohan/7th/454)

Q. A male of 75 years with cough, chest pain, hemoptysis and consolidation in the right upper lobe of lung. What is your clinical diagnosis? Write the differentials and investigations needed. (DU-18Ja)

Ans.

Clinical diagnosis: Right-sided pneumonic consolidation.

Differential diagnosis:

1. Lung abscess
2. Bronchiectasis with secondary infection

3. Pleural effusion
4. Pulmonary infarction.

Investigations: *Please write from above.*

Q. A 60 years man presented with haemoptysis and chest x-ray shows a consolidation in right lung. What is your differential diagnosis and what are the possible laboratory tests to evaluate it? (CU-18Nv)

Q. A 62 years old male having cough with expectoration. Radiological findings show consolidation in right lung. Write the possible causes and how you will investigate for diagnosis? (CU-16Ju)

Ans.

Possible causes / differential diagnosis:

1. Pneumonia
2. Lung abscess
3. Bronchiectasis with secondary infection
4. Pleural effusion
5. Pulmonary infarction.

Investigations for diagnosis / laboratory tests: *Please write from above.*

Lung Abscess

Q. Short note: Lung abscess. (DU-19Nv)

Ans.

Lung abscess: It is the **localized area of suppuration** within the **lung parenchyma** that leads to **parenchymal destruction** & manifested ***radiologically*** as **cavity with air-fluid level.**

Or,

The term *pulmonary abscess* describes a **local suppurative process** that produces **necrosis of lung tissue.**

(Ref: Robbins/10th/711)

Causes:

1. **Aspiration of infective material** (the most frequent cause)**:** Risk factors include-
   - Suppressed cough reflexes (e.g. acute alcohol intoxication, opioid abuse, coma, anesthesia, seizure disorders)
   - Severe dysphagia (e.g. neurologic deficits, esophageal disease)
   - Protracted vomiting
   - Poor dental hygiene.

   Aspiration first causes ***pneumonia***, which progresses to ***tissue necrosis*** and formation of ***lung abscess***.
2. **Antecedent primary lung infection:** Postpneumonic abscess formation (usually associated with *S. aureus, K. pneumoniae,* and pneumococcus).
3. **Septic embolism:** Infected emboli may arise from thrombophlebitis of the systemic venous circulation or from the vegetations of infective bacterial endocarditis on the right side of the heart.
4. **Bronchial obstruction:** By bronchogenic carcinoma, adenoma, foreign body (postobstructive pneumonia).
5. **Local spread:** Direct extension of suppurative infections from the esophagus, spine, pleural avity, liver abscess, subphrenic abscess.
6. **Haematogenous spread** from other sites of infection as pelvic abscess, pyemia, or septicaemia.
7. **Miscellaneous:** Traumatic penetrations of the lungs.

Causative organisms: Under appropriate circumstances any bacterial pathogen can produce an abscess; but the most common organisms include- **(For VIVA)**

1. Aerobic and anaerobic streptococci
2. *Staphylococcus aureus*
3. *Pseudomonas*
4. *Klebsiella*
5. *Proteus*
6. Anaerobic organisms normally found in the oral cavity (e.g. *Bacteroides*, *Fusobacterium*, and *Peptococcus* etc.)

Morphology:

- Abscesses vary in diameter from a **few millimeters** to **large cavities of 5 to 6 cm.**
- They may affect any part of the lung and may be **single** or **multiple.**
- **Cardinal histologic change** in all abscesses is **suppurative destruction of the lung parenchyma** within the **central area of cavitation.**
- Continued infection leads to large, poorly demarcated, fetid, green-black, multilocular cavities designated gangrene of the lung.
- **In chronic cases** considerable fibroblastic proliferation produces a **fibrous wall.**

Clinical features:

1. Cough with copious amounts of foul-smelling purulent or sanguineous sputum
2. Fever, chest pain, and weight loss
3. Occassional haemoptysis
4. Clubbing of the fingers and toes
5. Radiographic evidence of a fluid-filled cavity.

Complication: ***(For VIVA)***

- Extension of the infection into the pleural cavity
- Hemorrhage
- Development of *brain abscesses* or *meningitis* from septic emboli
- Secondary amyloidosis (in chronic long-standing cases).

(Ref: Robbins/10th/711; Harsh Mohan/7th/457; BRS Pathology/5th/213; Lecture SSMC)

Pulmonary Tuberculosis

Tuberculosis is a **chronic pulmonary** and **systemic disease** caused most often by ***M. tuberculosis***, and the leading infectious cause of death worldwide.

The **source of transmission** is **humans with active tuberculosis** who **release mycobacteria into the sputum.**

Tuberculosis flourishes wherever there is poverty, crowding, and chronic debilitating illness. In the United States, tuberculosis is mainly a disease of older adults, immigrants from high-burden countries, those living in crowded settings (prisons, homeless shelters, long-term care), and people with AIDS. Certain disease states also increase the risk: diabetes, Hodgkin lymphoma, chronic lung disease (particularly silicosis), chronic renal failure, malnutrition, alcoholism, and immunosuppression.

It is important that infection with *M. tuberculosis* be differentiated from active disease. Infection refers to the presence of bacteria in the body, which may be symptomatic (**active disease**) or not (**latent infection**). Most infections are acquired by **person-to-person transmission** of airborne organisms from an active case to a susceptible host.

(Ref: Robbins/10th/368)

Q. What are the types of pulmonary TB? Discuss the pathogenesis of primary pulmonary tuberculosis. (SU-15/10Ja)

Q. Give in short the pathogenesis of pulmonary tuberculosis. (DU-06M)

Ans.

Types of pulmonary tuberculosis:

1. Primary pulmonary tuberculosis
2. Secondary pulmonary tuberculosis *(occurs in an individual who has been previously infected by M. tuberculosis).*

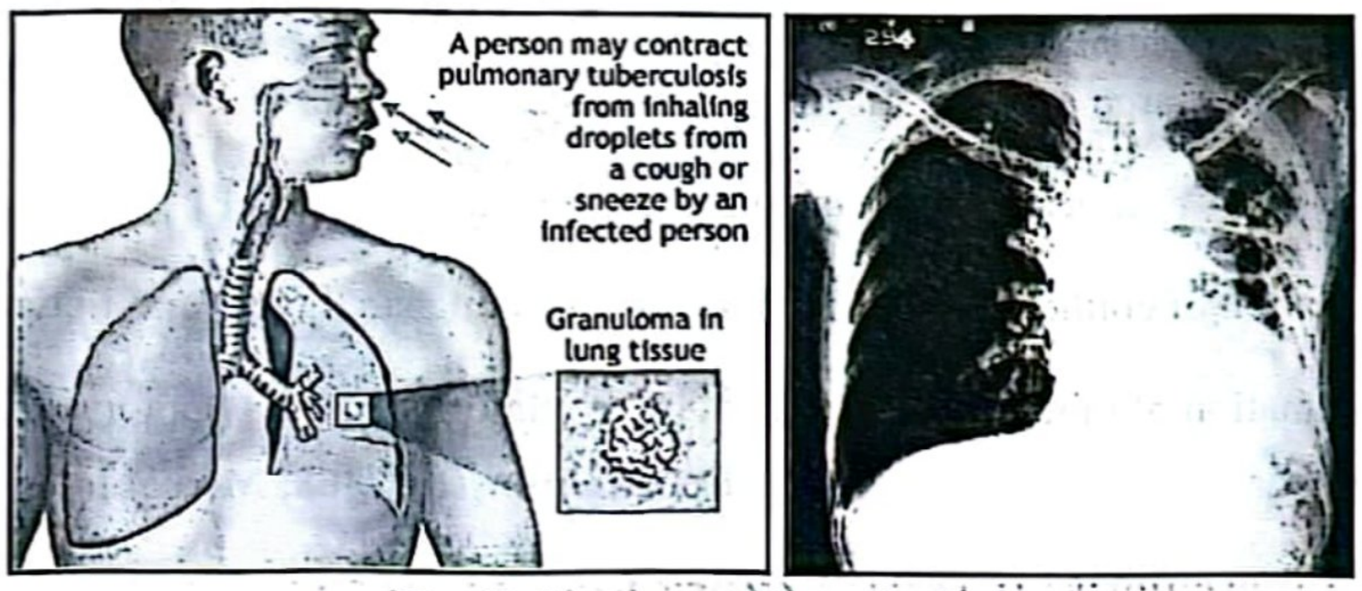

A person may contract pulmonary tuberculosis from inhaling droplets from a cough or sneeze by an infected person
Granuloma in lung tissue

Fig: Pulmonary tuberculosis.

Pathogenesis of pulmonary tuberculosis: Depends on the virulence of the organism, and two major immunological response of the individual's-

1. Acquired cellular immunity &
2. Delayed type hypersensitivity.

Primary infection:

Inhalation of droplet nuclei containing tubercle bacilli

↓

Organisms reach alveoli of the lung

↓

The bacteria are non-specifically taken up by alveolar macrophages

↓

But the inactivated macrophages are not able to destroy the organisms

↓

Organisms multiply within inactivated macrophages until the macrophages burst

↓

Other alveolar macrophages and the monocytes begin to extravasate from peripheral blood to the site of infection by chemotactic factor (they are also inactivated and hence cannot destroy the organisms)

↓

Multiply within it

↓

Spread to regional lymph nodes (hilar lymph nodes)

↓

Lymphangitis

↓

Enlargement of hilar lymph nodes

↓

Primary Ghon's complex

↓

Spread to the blood stream

↓

Gives rise to military tuberculosis affecting various organs of body.

Secondary infection (re-infection):

Macrophage activating response due to cell mediated immunity
↓
Sensitized T-cell secretes lymphokine
↓
Lymphokine activates macrophages that are capable of killing and digesting the bacilli
↓
Macrophage secretes cytokines
↓
Accumulation of large number of activated macrophage at the site of primary lesion
↓
Macrophage transforms into epithelioid cell
↓
Aggregation of epithelioid cells form giant cell (Langhan's type) and fibrosis
↓
Formation of tubercle & manifestation of clinical signs & symptoms.

(Ref: Robbins/10th/368; Microbiology Lecture, SSMC)

Q. What is primary tuberculosis? (CU-04S) ***(Very Important for VIVA)***
Q. What are the primary sites of tuberculosis? (CU-04S)
Q. What is Ghon's focus and Ghon's complex? (DU-14Ja, SU-15Ja,12Ju)
Q. Short note: Ghon's focus and Ghon's complex. (DU-17M,13Ja)
Q. Short note: Ghon's complex. (DU-18Ja)
Ans.
Primary tuberculosis: Primary tuberculosis is the form of disease that develops in a previously unexposed and therefore unsensitized person.

(Ref: Robbins/10th/369)

Primary tuberculosis occurs after initial infection (first exposure) with *Mycobacterium tuberculosis* or *Mycobacterium bovis*. About 5% of newly infected people develop clinically significant disease. Rest 90-95% cases of primary TB remain asymptomatic (fever, malaise). Source of organism is exogenous here in primary TB.

(Ref: Robbins/10th/369)

Primary sites of tuberculosis: ***(Very Important for VIVA)***

1. Lungs (mainly)
2. Intestine
3. Skin
4. Oropharyngeal &
5. Lymphoidal

Ghon's complex: It is the ***lesion of primary tuberculosis*** and consists of- ***(Very Important for VIVA)***

i) **Ghon's focus:** The focus / site of the lung which is affected primarily by the tubercle bacilli, is called Ghon's focus.
ii) **Lymphangitis**
iii) **Hilar lymphadenitis** (inflammation of the lymph nodes of the hillum of the lungs).

(Ref: Robbins/10th/371; Lecture SSMC)

Q. Can primary tuberculosis occur more than once? ***(V.V.I for VIVA)***
Ans.
Yes, primary tuberculosis can occur more than once.

- In elderly & in profoundly immuno-suppressed
- They loose their immunity to TB bacilli & so develop primary TB more than once (source of organism is exogenous always)
- Most people go on to have latent disease
- Progressive infection with continued pathology occurs in some & diagnosis of "progressive primary TB" in adult can be difficult.

(Ref: Lecture SSMC)

Q. What are the fates of primary tuberculosis in lung? (DU-14Ja)
Q. Mention the fate of primary pulmonary tuberculosis.
Q. Mention the fate of Ghon's focus.
Ans.

Fates of primary pulmonary tuberculosis: ***(Very Important for VIVA)***

1. Complete resolution
2. Healing with fibrosis & calcification
3. Progressive pulmonary tuberculosis (/ disseminated military tuberculosis)
4. Progresses to secondary tuberculosis (re-infection).

(Ref: Robbins/10th/369; Lecture SSMC)

Q. What is secondary tuberculosis?
Ans.
Secondary tuberculosis: Secondary tuberculosis is the form of the disease that develops in a previously sensitized host.

(Ref: Robbins/10th/370)

It may follow shortly after primary TB, but more commonly it arises from **reactivation** of dormant primary lesion months to years after the initial infection, particularly when host resistance is weakened. It may also result from exogenous **re-infection** because of waning of protection afforded by primary diseases or because of a large inoculum of virulent bacilli.

Reactivation is more common in ***low-prevalence areas***, and **reinfection** plays an important role in ***regions of high contagion***.

(Ref: Robbins/10th/370; Lecture SSMC)

Q. What are the sites of primary and secondary tuberculosis in lung? (DU-14Ja) ***(Very Important for VIVA)***
Ans.
Sites of primary tuberculosis in lung: Sub-pleural region (lower part of the upper lobe or the upper part of the lower lobe).

(Ref: Robbins/10th/369)

Sites of secondary tuberculosis in lung: Apex of the upper lobe of one or both lungs, because of high oxygen tension promotes growth of bacteria.

(Ref: Robbins/10th/370)

Q. What are the differences between primary and secondary tuberculosis? (SU-12Ju)
Ans.

Differences between primary and secondary tuberculosis: ***(Very Important for VIVA)***

Traits	Primary tuberculosis	Secondary tuberculosis
1. Affected person	Previously unexposed	Previously exposed
2. Source of infection	Exogenous	Both exogenous and endogenous
3. Site	Sub-pleural lesion (lower part of	Apex of the upper lobe *(one or both*

	the upper lobe or the upper part of the lower lobe)	*lungs, usually in right lung)*
4. Sign/symptoms	Mostly asymptomatic	Symptomatic
5. Cavitation	Less common	More common
6. Caseation	Less common	More common
7. Lymph node involvement	More common	Less common

(Ref: Robbins/10th/370; Lecture SSMC & DMC)

Q. Mention the sites where tuberculosis does not occur? *(For VIVA)*

Ans.

Sites where tuberculosis does not occur:

- Skeletal muscle
- Cardiac muscle
- Thyroid gland.

Q. Define miliary tuberculosis. (DU-09Ja) ***(Very Important for VIVA)***

Ans.

Military tuberculosis: In some cases, bacilli within the macrophage spread to **regional lymph node** in the hilum of the lung and thence to the **blood stream**, which in turn **distributes the organisms to almost all parts of the body**. It is called miliary tuberculosis.

(Ref: Microbiology Lecture, SSMC)

Miliary tuberculosis is most prominent in the liver, bone marrow, spleen, adrenals, meninges, kidneys, fallopian tubes & epididymis, but can involve any organ. It occurs when the body immunity fails to control the primary infection.

(Ref: Robbins/10th/373)

Q. Write down the pathology / morphology of pulmonary tuberculosis.

Q. Discuss the pathological characteristics of secondary pulmonary tuberculosis. (DU-09Ja)

Ans.

Pathology / morphology of pulmonary tuberculosis:

Primary pulmonary tuberculosis:

i) There is a focal lesion in the lung called Ghon's focus
ii) Lymphangitis and enlargement of hilar lymph nodes
iii) Ghon's focus, together with nodal involvement (lymphangitis and lymphadenitis) is called the Ghon's complex
iv) The Ghon's focus gradually gets healed up and calcified (Ghon's body)
v) If the infection is not contained, the organisms may reach the blood stream causing systemic tuberculosis affecting various organs (milliary tuberculosis).

Secondary pulmonary tuberculosis:

***Gross*:**

1. Lesion is located in the apex of one or both lungs
2. It begins as a small focus of consolidation, usually <3 cm
3. Initial lesion may be located in the other region of the lung
4. In almost every cases of re-infection, the regional nodes develop foci of similar tubercular lesion

***Microscopic*:**

1. Accumulation of large number of activated macrophage at the site of primary lesion and the formation of tubercle
2. The tubercle comprises an organized aggregation of activated macrophages; because they resemble epithelial cells, they are called epithelioid cells
3. Epithelioid cells have a pale, pink, granular cytoplasm

4. Epithelioid cells fuse to form giant cells
5. These giant cells may attain diameters of 40-50 μm. They comprise a large mass of cytoplasm containing 20 or more small nuclei arranged either peripherally (Langhans-type giant cell) or haphazardly (Foreign-body type giant cell)
6. A peripheral collar of fibroblast, lymphocyte, and macrophage surrounds the granuloma
7. Sometimes the central part of the granuloma undergoes characteristic caseous necrosis to produce a soft tubercle, the characteristic hallmark of TB.

(Ref: Microbiology Lecture, SSMC; Robbins/10th/100,371)

Q. Describe in short the pathogenesis of tubercular granuloma. (CU-09Ja,08Ja)
Q. Give the immunopathogenesis of TB granuloma. (DU-03Ja)
Q. Give the histological features of granuloma. (RU-12Ja)
Q. Draw and label soft tubercle. (SU-03M/Ja) **Write the morphology of soft tubercle.**
Q. Draw and label the microscopic appearance of tubercular lymph node / TB lymphadenitis.
Ans.

Formation of tubercle: With the development of specific immunity and accumulation of large number of activated macrophage at the site of primary lesion, the initial non-specific response becomes granulomatous evoking the formation of tubercle.

Immuno-pathogenesis /mechanism of formation of TB granuloma / soft tubercle:

Causative agent of granuloma (infectious agent or immunological agent)
↓
Polymorphonuclear cells (neutrophils) come at the site of infection
↓
After 24 hours, macrophages come at the site of infection
↓
When the inciting agent is poorly degradable or particulate, macrophages engulf the foreign material and process and present some of it to appropriate T lymphocytes, causing them to become activated
↓
The responding T cells produce cytokines, such as IL-2, which activates other T cells perpetuating the response and IF-γ, which is important in activating macrophages and transforming them into epithelioid cells & multinucleated giant cells.
↓
There is also accumulation of lymphocytes, fibroblasts and plasma cell
↓
Caseation necrosis occurs
↓
Caseating granuloma / soft tubercle.

Morphology of tubercle:

1. The tubercle comprises an organized aggregation of activated macrophages; because they resemble epithelial cells, they are called epithelioid cells
2. Epithelioid cells have a pale, pink, granular cytoplasm
3. Epithelioid cells fuse to form giant cells
4. These giant cells may attain diameters of 40-50 μm. They comprise a large mass of cytoplasm containing 20 or more small nuclei arranged either peripherally (Langhans-type giant cell) or haphazardly (Foreign-body type giant cell)
5. A peripheral collar of fibroblast, lymphocyte, and macrophage surrounds the granuloma
6. Sometimes the central part of the granuloma undergoes characteristic caseous necrosis to produce a soft tubercle, the characteristic hallmark of TB.

(Ref: Microbiology Lecture, SSMC; Robbins/10th/100,371)

Q. Mention the common clinical features of pulmonary TB. (For VIVA)

Ans.

Clinical features of pulmonary TB:

1. Systemic symptoms include malaise, anorexia, weight loss, and fever.
2. Fever is low grade and remittent (appearing late each afternoon and then subsiding)
3. Night sweats
4. Cough with sputum production (at first mucoid and later purulent)
5. Some degree of hemoptysis is present in about one-half of all cases
6. Pleuritic chest pain may be present
7. Extrapulmonary manifestations of tuberculosis are legion and depend on the organ system involved.

(Ref: Robbins/10th/370)

Q. How you can diagnose a case of pulmonary TB? (For VIVA)

Q. How will you investigate pulmonary tuberculosis? (BUP-22Nv)

Ans.

Diagnosis of pulmonary TB:

1. History and physical examination
2. Radiologic findings of consolidation or cavitation in the apices of lung
3. AFB staining and culture of sputum - ***gold standard*** (culture on *solid agar media* shows growth at 3 to 6 weeks, but culture in *liquid media* can provide an answer within 2 weeks)
4. ESR- *High*
5. PCR amplification of *M. tuberculosis* DNA – **GeneXpert** *{can detect as few as 10 organisms in clinical specimens, e.g. pleural, ascitic, pericardial, joint fluid & CSF compared to >10,000 organisms required for smear positivity (AFB)}*
6. Antibiotic susceptibility test (C/S) (*as multi-drug resistance is common now*)
7. MT test / tuberculin skin test (*not diagnostic*).

(Ref: Robbins/10th/371; Lecture SSMC)

Q. Short note: Mantaux / tuberculin test. (DU-07Ju) **(For VIVA)**

Ans.

Mantoux / tuberculin test: Infection with *M. tuberculosis* typically leads to development of delayed hypersensitivity to *M. tuberculosis* antigen which can be detected by this test.

This test has no diagnostic value and only indicates the occurrence of past and recent infection when the reaction is positive. The test becomes positive about 2-4 weeks after infection.

Reagent: Purified protein derivatives (PPD). WHO recommended tuberculin is "PPD-RT-23 with Tween 80".

Dose: 5 tuberculin units (TU) – 0.1 ml.

Technique of injection: 0.1 ml PPD is slowly injected on the flexor aspect of the forearm intradermally.

Reaction: Visible & palpable induration, that peaks in 48-72 hours.

Reading: Reading is taken after 72 hours (3rd days). Induration is measured in mm.

Interpretation:

1. **Positive reaction:** Induration **exceeding 10 mm.** (it indicates that, the person is infected with *M. tuberculosis*; it dose not prove that the person is suffering from the disease, i.e. a positive tuberculin test does not differentiate between infection and active disease).
2. **Negative reaction:** Induration **less than 6 mm.**
3. **Doubtful reaction:** Induration **between 6 and 9 mm.** (Here the reaction may be due to *M. tuberculosis* or atypical mycobacteria).

False positive reaction:

- Prior BCG *(Bacillus Calmette-Guerin)* vaccination

- Atypical mycobacterium infection

False negative reaction:

- Viral infections (e.g. HIV, measles, chicken pox)
- Sarcoidosis
- Malnutrition
- Malignancy
- Hodgkin lymphoma
- Immunosuppression
- Overwhelming active tuberculosis
- Incorrect injection of PPD.

(Ref: Robbins/10th/371; Park/25th/197; Lecture SSMC)

Q. A male of 30 years presented with evening rise of fever, cough and cervical lymphadenopathy. What is your provisional diagnosis? Write down the laboratory investigations to establish the diagnosis. (DU-22M)

Ans.

Provisional diagnosis: Pulmonary tuberculosis.

Laboratory investigations to establish the diagnosis: *Please write from above.*

Q. A man aged 28 years came with history of low grade evening rise of temperature, gradual weight loss and right cervical lymphadenopathy. What are the possible causes and how you are going to diagnose the case? (RMU-21M)

Ans.

Possible causes:

1. Tuberculosis
2. Lymphoma
3. HIV infection

Diagnostic approach:

1. CBC with PBF
2. ESR
3. Serum LDH
4. Serum ADA.
5. Chest X-ray P/A view
6. AFB staining and culture of sputum (if any) - *gold standard for TB*
7. GeneXpert
8. MT test
9. HIV serology
10. Biopsy (excisional or core) from the enlarged cervical lymph node followed by histopathology and IHC (if needed) – confirmatory.

Q. A male 20 years presented to the CPD with evening rise of fever, cough and cervical lymphadenopathy. What is your provisional diagnosis? What test can you do on the lymph node to establish the diagnosis? (DU-17Ja)

Ans.

Provisional diagnosis: Pulmonary tuberculosis.

Test for the lymph node to establish the diagnosis: FNAC or biopsy from the lymph node.

Q. A diabetic 50 years old male presented with chronic cough and haemoptysis. Chest x-ray shows apical opacity and transbronchial biopsy reveals granuloma. What is the most likely diagnosis? Is their any chance of widespread dissemination in this patient? (DU-07Ja)

Ans.

Most likely diagnosis: Pulmonary tuberculosis (secondary).

Chance of wide spread dissemination: Normally secondary tuberculosis spreads locally, not by lymphatic or haematogenous route. But if there is inadequate treatment or impaired host defense (that may occur to this patient, as he is diabetic) organisms may seed into lymphatics or pulmonary venous system. In first case organisms reach via lymphatic system to the right heart and cause miliary pulmonary disease. In later case, organisms reach the right ventricle and cause systemic miliary tuberculosis.

Q. 28 years male having illness for 6 months. Cervical lymph node is non-tender, firm, and matted. What is your provisional diagnosis? ***(Important for VIVA)***

Ans.

Provisional diagnosis: Pulmonary tuberculosis.

Q. A female of 56 years has presented with dry cough for more than one month, weight loss, and anorexia. His X-ray chest P/A view reveals an ill-defined opacity in right apical region. What is your probable diagnosis? How will you confirm your diagnosis?

Ans.

Probable diagnosis: Pulmonary tuberculosis.

Confirmation of diagnosis: Sputum culture for acid-fast bacillus.

Lung Tumors

Q. Classify lung tumours. (DU-23M,21Ja,20Nv/M,16Ju,04Ja, SMU-23M, CMU-23/22/21M, 20Nv/Ju,15Ja,11/ 09/08Ju)

Ans.

Classification of lung tumors:

A. Benign:
- Adenoma
- Fibroma
- Leiomyoma
- Lipoma
- Haemangioma
- Haemangiopericytoma
- Chondroma

B. Malignant: ***(For VIVA)***

1. **Primary:**
   - Bronchogenic carcinoma *(90-95%)*
   - Bronchial carcinoid *(about 5%)*
   - Fibrosarcoma
   - Leiomyosarcoma
   - Hodgkin's and Non-Hodgkin's lymphoma
2. **Secondary** (*more common than primary tumors*): Particularly from carcinoma of **breast, colon, kidney, uterus, ovary, testes, thyroid,** and also from **osteogenic** and **other sarcomas.**

C. Tumor like lesion: *(For VIVA)*

1. Hamartoma
2. Eosinophilic granuloma.

(Ref: Robbins/10th/673,715; Davidson's/23rd/603; Pathoma Lecture Notes; Lecture SSMC)

Q. Write the histologic classification of malignant epithelial tumours of the lungs. (CU-16Ja,13Ju)
Q. Give the WHO classification of bronchogenic carcinoma. (DU-18Nv)
Q. Give the histomorphological classification of bronchogenic carcinoma. (RU-12Ju, SU-08Ju,05Ja, CU-05Ja)
Q. Classify bronchogenic carcinoma. (RMU-22/21/20/19Nv,18Nv/Ja,17Nv/Ja,14Ju,11Ja, SUST-21Nv,19Nv/M,17M, 16Ja,14/13Ju)
Ans.

Histologic classification (WHO) of malignant epithelial lung tumours (bronchogenic carcinoma):

1. **Adenocarcinoma** (acinar, papillary, micropapillary, solid, lepidic, and mucinous adenocarcinoma)
2. **Squamous cell carcinoma**
3. **Large cell carcinoma**
4. **Neuroendocrine carcinoma**
   - Small cell carcinoma
   - Large cell neuroendocrine carcinoma
   - Carcinoid tumor (typical, atypical)
5. **Mixed carcinomas**
   - Adenosquamous carcinoma
   - Combined small cell carcinoma
6. **Other unusual morphologic variants**
   - Sarcomatoid carcinoma
   - Spindle cell carcinoma
   - Giant cell carcinoma.

{Ref: Robbins BASIC PATHOLOGY/10th/538 (2015 WHO Classification, Simplified Version)}

Nice to Know: *(V.V.I. For VIVA)*

For therapeutic purposes, lung carcinomas are often sub-classified into:

1. **Small cell lung cancer (SCLC)** (15% of all lung carcinoma) – Usually not considered amenable to surgery. Best treated with ***chemotherapy***.
2. **Non-small cell lung cancer (NSCLC)** (85% of all lung carcinoma) – ***Surgical*** intervention may be considered if limited to the lung.
   - Adenocarcinoma (most common – 35-40%)
   - Squamous cell carcinoma
   - Large cell carcinoma
   - Carcinoid tumor.

(Ref: Robbins BASIC PATHOLOGY/10th/538 + 10th/717; BRS Pathology/5th/217; Davidson's/23rd/599; Pathoma Lecture Notes)

Malignant tumors of the lung:

Primary:		
Type	**Location**	**Characteristics**
Adenocarcinoma	Peripheral	▪ Most common cancers overall (35-40%) ▪ Most common type in **women** and in **non-smokers** as well as **female smokers** ▪ Have been associated with mutations in the EGFR gene

Squamous cell carcinoma	Central	▪ Occur almost exclusively in **smokers** ▪ Most common tumor in **male smokers** ▪ Associated with "**double C**" - HyperCalcemia (due to PTHrp) - Cavitation
Small cell carcinoma (formerly known as "**oat cell**" carcinomas)	Central	▪ Shows the **strongest association with smoking** (99% of small cell carcinoma patients are smokers) ▪ **Most aggressive** bronchogenic carcinoma ▪ Usually already **metastatic at diagnosis** ▪ Least likely form to be cured by surgery
Large cell carcinoma	Peripheral	▪ More common in men ▪ Have strong association with cigarette smoking ▪ Highly malignant ▪ Tumour cells typically have have large nuclei, prominent nucleoli, and abundant cytoplasm
Carcinoid tumor	Central or peripheral	▪ Not related to smoking ▪ Most common primary lung cancer in children ▪ Slow-growing, indolent tumors which do not metastasize and have excellent prognosis with appropriate surgery (5-year survival: 90%).
Secondary:		
Carcinoma metastatic to the lung		▪ More common than primary tumors ▪ Canon-ball nodules on imaging (x-ray)

(Ref: Robbins BASIC PATHOLOGY/10th/538,539 + 10th/716; BRS Pathology/5th/216-218; Davidson's/23rd/599; Harsh Mohan/7th/481; Pathoma Lecture Notes)

*(N.B: **Central/hilar** = Lung cancer arises in the **main bronhus** or one of its **segmental branches*** in the hilar parts of the lung.

***Peripheral** = Lung cancer originates from a **small peripheral bronchiole** but the exact site of origin may not be discernible.)*

Q. What are the primary sites causing secondaries in lung? (V.V.I. for VIVA)

Ans.

Primary sites from where carcinoma metastasizes to lung: Remember the formula PUB-LIK-T

P = Prostate
U = Uterus
B = Bronchus (opposite lung), breast, bone
L = Liver
I = Intestine (carcinoma colon, caecum)
K = Kidney
T = Testis (teratoma, seminoma), thyroid.

Q. What do you mean by bronchogenic carcinoma? (DU-08Ja) **Give the aetiopathogenesis of bronchogenic carcinoma.** (SMU-23M, CMU-22Nv, RU-12Ju)
Q. Write the risk factors of bronchogenic carcinoma. (SU-14Ja)
Q. Give the aetiology (CU-05Ja, SU-05Ja) **& pathogenesis of bronchogenic carcinoma.**
Q. Write briefly the etiopathological factors responsible for bronchogenic carcinoma. (SU-08Ju)

Ans.

Bronchogenic carcinoma: Bronchogenic carcinoma refers to the **malignant neoplasm of the lung** arising from the **bronchial epithelium** or **mucous glands**.

Or,

The term **bronchogenic carcinoma** is commonly used for cancer of the lungs which includes carcinomas arising from the **respiratory epithelium** lining the **bronchi, bronchioles** and **alveoli**.

It is the **most frequently diagnosed cancer** in the world and the **most common cause of cancer mortality** worldwide; occurs most often between ages 40 and 70 years, with the peak incidence in the 50s or 60s.

(Ref: Davidson's/23rd/599; BRS Pathology/5th/215,216; Robbins/10th/715)

Aetio-pathogenesis / risk factors of bronchogenic carcinoma:

1. **Tobacco smoking** (most important cause): 85% to 90% of lung cancers arise in smokers, and the most common tumors in smokers are small cell and squamous cell carcinomas. Risk directly linked to duration and amount of smoking (pack years).
2. **Air pollution:** Indoor air pollution, especially by ***radon*** (2nd most common cause).
3. **Radiation exposure:** High-dose **ionizing radiation**, especially in **radium** and **uranium** workers.
4. **Asbestos:** Increased incidence of lung cancer with asbestos and greater increase with combination of asbestos and cigarette smoking.
5. **Industrial hazards:** Such as ***nickel***, ***chromium***, ***beryllium***, ***arsenic***, ***vinyl chloride*** and ***mustard gas*** etc.
6. **Molecular genetics:** Dominant oncogenes that are frequently involved in lung cancer include *c-MYC, K-RAS, EGFR* and *HER-2/neu.*
7. **Precursor (pre-invasive) lesions:** Four types of morphologic precursor epithelial lesions are recognized:
   a. Squamous dysplasia and carcinoma in situ
   b. Atypical adenomatous hyperplasia
   c. Adenocarcinoma in situ
   d. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia.

(Ref: Robbins BASIC PATHOLOGY/10th/538 + 10th/716; BRS Pathology/5th/216)

Nice to Know: Very very Informative

Relationship between tobacco smoking and lung cancer:

- **Lung carcinoma** is the **leading cause of death from cancer** in **both men and women.**
- Majority **(85% to 90%)** of lung cancers arises in **smokers**, and the **most common** tumors in **smokers** are **small cell** and **squamous cell carcinomas.** The incidence of these tumors is directly proportional in incidence to the number of cigarettes smoked daily and to the number of years of smoking (pack year). In contrast, **lung cancers in never-smokers** are most likely to be **adenocarcinomas.**
- **Squamous cell carcinoma** is the **most common** lung cancer in **male smokers**, whereas **adenocarcinoma** is the **most common** lung cancer in **non-smokers** and **female smokers.**
- Compared with non-smokers, **average smokers** of cigarettes have a **10 fold** greater risk of developing lung cancer, and **habitual heavy smokers** (two packs a day for 20 years) have a **60-fold** greater risk.
- The **death rate** from the disease in **heavy smokers is 40 times** that in non-smokers.
- Risk falls slowly after smoking cessation but remains above that in non-smokers for many years.
- Cessation of smoking for 10 years reduces risk but never returns to the non-smoker level.
- Second-hand smoke, or environmental tobacco smoke, contains numerous human carcinogens for which there is no safe level of exposure.
- It is estimated that each year about 3000 nonsmoking adults die of lung cancer as a result of breathing secondhand smoke.

- More than 1200 substances have been counted in cigarette smoke, many of which are potential **carcinogens**. They include both **initiators** (***polycyclic aromatic hydrocarbons*** such as ***benzo[a]pyrene***) and **promoters**, such as ***phenol derivatives***.
- Epidemiologic studies also show an association between **cigarette smoking** and **carcinoma of the mouth, pharynx, larynx, esophagus, pancreas, uterine cervix, kidney,** and **urinary bladder.**

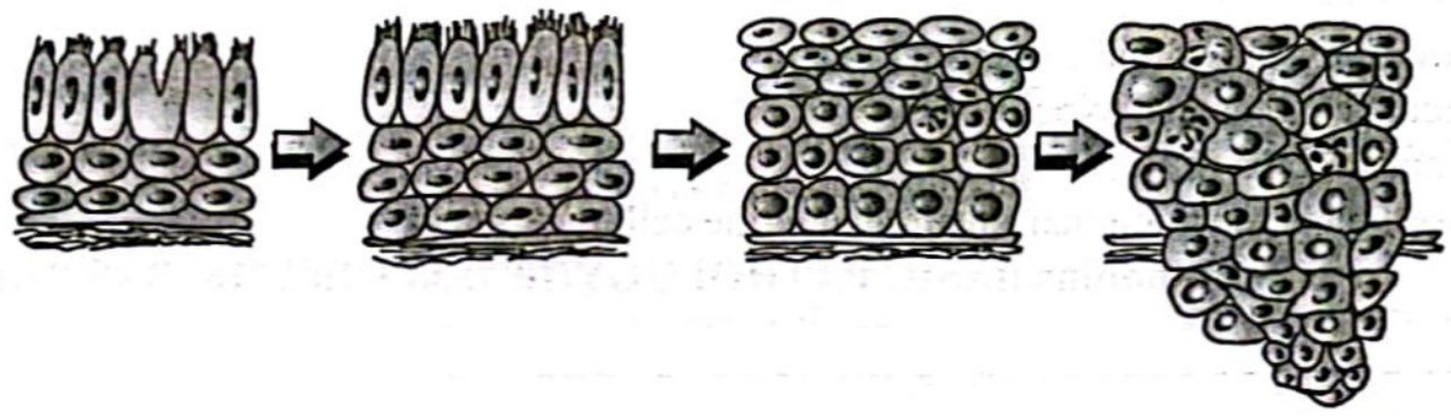
(Ref: Ref: BRS Pathology/5th/216; Robbins BASIC PATHOLOGY/10th/358 + 10th/716; Davidson's/23rd/599)

Q. Write down the morphology of bronchogenic squamous cell carcinoma. (CU-11Ju,06M)
Q. How cigarette smoking causes lung cancer? (RU-21/20Nv)
Q. Short note: Bronchogenic squamous cell carcinoma. (SU-15Ja, RU-08Ja)
Ans.

Bronchogenic squamous cell carcinoma: Bronchogenic squamous cell carcinoma is **most commonly found** in **men** and is strongly associated with **smoking**. It is the **most common** lung cancer in **male smokers.**

These tumours usually arise in a **large bronchus** and are prone to massive **necrosis** and **cavitation.**

Pathogenesis: Chronic smoking → ***Chronic irritation*** in the columnar ciliated lining epithelium of the respiratory tract → ***Squamous metaplasia*** (columnar cells are replaced by stratified squamous epithelium) → ***Dysplasia → Carcinoma in situ → Invasive squamous cell carcinoma.***



A, NORMAL BRONCHIAL MUCOSA | B, BASAL CELL HYPERPLASIA | C, SQUAMOUS METAPLASIA AND DYSPLASIA | D, CARCINOMA *IN SITU* WITH MICROINVASION

Morphology:

Macroscopic:

- **Location:** Central (most often around the hilum of lung).
- **Types:** Three types of growth pattern - fungating, infiltrative & cauliflower-like.
- **Colour:** Gray-white.
- **Consistency:** Firm to hard.
- Large lesions may undergo **central necrosis,** giving rise to **cavitation.**

Microscopic:

- Presence of ***keratinization (keratin pearls)*** and/or ***intercellular bridges***.
- The tumour may show varying histologic grades of differentiation such as ***well-differentiated***, ***moderately-differentiated*** and ***poorly-differentiated***.
- Squamous ***metaplasia***, epithelial ***dysplasia***, and foci of ***carcinoma in situ*** may be seen in bronchial epithelium ***adjacent to the tumor mass***.

(Ref: Robbins BASIC PATHOLOGY/10th/539 + 10th/718; Harsh Mohan/7th/480)

Q. Write down briefly the morphology of small cell carcinoma of lung. (DU-08Ja, SU-14Ja, CU-08Ju)
Q. Write about small cell carcinoma. (CU-04S)
Ans.

Small cell carcinoma: (formerly known as ***"oat cell"*** carcinomas)

Characteristics:

1. About 15% of all bronchogenic carcinoma
2. Shows the strongest association with smoking (99% of small cell carcinoma patients are smokers)
3. Arise from neuroendocrine cells (Kulchitsky cells)
4. Highly malignant, rapidly growing tumour (there is no known preinvasive phase)
5. Early metastasis and inoperable at presentation
6. Usually responds to chemotherapy and radiotherapy, less likely to be cured by surgery
7. Overall prognosis is poor. Survival is short (3 months to 1 year).

Morphology:

Macroscopic:

- **Location:** Central/hilar (by the time of diagnosis, most will have metastasized to hilar and mediastinal lymph nodes).
- **Colour:** Pale-gray.

Microscopic:

1. Relatively **small** (or oat-like) **tumor cells** (round, oval, or spindle shaped) consisting:
   - Scant cytoplasm
   - Ill-defined borders
   - Finely granular nuclear chromatin ("**salt and pepper**" appearance)
   - Absent or inconspicuous nucleoli
   - Frequent nuclear molding
   - A high mitotic count.
2. These cells are organised into ***cords***, ***sheets***, ***aggregates*** and ***ribbons*** or around small blood vessels forming ***pseudorosettes***.

(Ref: Robbins BASIC PATHOLOGY/10th/539,540 + 10th/718; Pathoma Lecture Notes; Lecture CMC)

Q. Why small cell carcinoma is most dangerous? *(For VIVA)*

Ans.

Small cell carcinoma is most dangerous: Because:

1. Most aggressive lung tumor
2. Early wide-spread metastasis (mostly at the time of diagnosis)
3. Poor prognosis
4. Virtually incurable by surgical means (chemotherapy and radiotherapy is needed)
5. Almost invariably fatal.

(Ref: Lecture DMC)

Q. Name 5 paraneoplastic syndromes with lung carcinoma.

Q. Discuss the paraneoplastic syndromes related to bronchogenic carcinoma. (SU-19M,13Ju)

Ans.

Non-metastatic extrapulmonary manifestations (paraneoplastic syndromes) related to lung cancer / bronchogenic carcinoma: *(V.V.I. for VIVA)*

1. **Endocrine:**
   - SIADH, inducing hyponatraemia (*due to inappropriate ADH secretion*)
   - Cushing syndrome (*due to ectopic ACTH secretion*)
   - Hypercalcaemia (*due to secretion of PTH, parathyroid hormone-related peptide, prostaglandin E, and some cytokines*)
   - Hypocalcemia (*due to calcitonin*)
   - Gynaecomastia (*due to gonadotropins*)
   - Carcinoid syndrome (*due to serotonin and bradykinin*)
2. **Neurological:**
   - Lambert-Eaton myasthenic syndrome
   - Peripheral neuropathy
   - Myelopathy
   - Cerebellar degeneration

3. **Others:**
   - Digital clubbing
   - Hypertrophic pulmonary osteoarthropathy (HPOA)
   - Polymyositis and dermatomyositis
   - Acanthosis nigricans
   - Hematologic abnormalities, such as *leukemoid reactions*
   - Hypercoagulable states, such as *Trousseau syndrome* (deep vein thrombosis and thromboembolism)
   - Nephrotic syndrome.

(Ref: Robbins BASIC PATHOLOGY/10th/543 + 10th/722; Davidson's/23rd/601)

Q. Mention the clinical features of lung carcinoma. (For VIVA)
Q. How you will diagnose a case of bronchogenic carcinoma? (DU-23M,21Ja,20Nv/M)
Q. Mention the steps you will take in the diagnosis of bronchogenic carcinoma. (RU-18/17Nv,11Ja)
Q. Mention the laboratory diagnosis of bronchogenic carcinoma. (RU-19Nv,06S, CU-17M)
Q. Write down the investigations of a case of pulmonary neoplasm. (DU-18Nv)
Ans.

Steps of diagnosis of bronchogenic carcinoma: ***(V.V.I. for VIVA in Medicine also)***

History:
- **Age** (50s or older)
- **Cigarette smoking** (even passive smoking)
- **Exposure to other risk factors**, e.g. asbestos, silica, beryllium, cadmium, chromium, arsenic, iron oxide, radon, ionizing radiation, petroleum products and oils, coal tar, products of coal combustion etc.

Clinical features:

1. **Local symptoms:**
   - Cough (most common early symptom; often dry, may be productive)
   - Chest pain
   - Dyspnoea
   - Hemoptysis
2. **Bronchial obstructive symptoms:** Occlusion of a bronchus may result in:
   - Bronchopneumonia
   - Lung abscess
   - Bronchiectasis
   - Pleural effusion
3. **Symptoms due to local spread in mediastinum:**
   - Hoarseness of voice
   - Dysphagia
   - Superior vena cava obstruction syndrome (SVCO)
   - Horner's syndrome
4. **Symptoms due to metastasis** (most commonly in **liver, brain, bone, adrenal, skin, contralateral lung** and **lymph nodes**)**:** Symptoms of metastases depend on the site, for example:
   - Back pain in bone metastases
   - Headache, hemiparesis, cranial nerve damage, and seizures in brain metastases.
5. **Symptoms due to non-metastatic extrapulmonary manifestations** (paraneoplastic syndromes).
6. **General features of malignancy:** Anorexia, weight loss, malaise, fatigue.

(Ref: Davidson's/23rd/599; BRS Pathology/5th/216; Robbin's/10th/721; Harsh Mohan/7th/483)

Laboratory investigations: ***(V.V.I. for VIVA in Medicine also)***

1. **To confirm the diagnosis:**

- **X-ray chest P/A view** (findings may be lobar collapse, mass lesions, effusion or malignant rib destruction)
- **CT scan of chest**
- **Bronchoscopy and biopsy** followed by histopathology – in case of central lesions
- **Image** (CT / USG) **guided percutaneous needle biopsy** followed by histopathology – in case of peripheral lesions
- **Sputum cytology for malignant cells** (exfoliative cytology) – for those who are unfit for invasive investigations
- **FNAC (or biopsy) of affected lymph nodes** (if any)
- In patients with pleural effusion - **pleural aspiration and biopsy**

2. **To see the evidence of metastasis** (for staging purpose):
   - USG of whole abdomen
   - CT scan of chest, abdomen and pelvis
   - Whole body isotope bone scan
   - MRI of brain
   - PET-CT scan.

3. **Others (base line investigations):**
   - CBC
   - Liver function test (LFT), renal function test (RFT) (before chemotherapy, if needed)
   - Pulmonary function test specially FEV_1.

(Ref: Davidson's/23rd/601; Prof. ABM Abdullah/Long Cases in CLINICAL MEDICINE/117)

Fig: Chest x-ray P/A view showing large cavitated lung cancer in left lower lobe.

Nice to Know:

Local effects of lung tumor spread:

Clinical Feature	Pathologic Basis
Cough (50%-75%)	Involvement of central airways
Hemoptysis (25%-50%)	Hemorrhage from tumor in airway
Chest pain (20%)	Extension of tumor into mediastinum, pleura or chest wall
Pneumonia, abscess, lobar collapse	Airway obstruction by tumor
Lipoid pneumonia	Tumor obstruction; accumulation of cellular lipid in foamy macrophages
Pleural effusion	Tumor spread into pleura
Hoarseness	Recurrent laryngeal nerve invasion
Dysphagia	Esophageal invasion
Diaphragm paralysis	Phrenic nerve invasion
Rib destruction	Chest wall invasion
SVC syndrome	SVC compression by tumor
Horner syndrome	Sympathetic ganglia invasion
Pericarditis, tamponade	Pericardial involvement

(Ref: Robbin's/10th/722)

Q. Tell 1 possible complication of percutaneous needle biopsy of lung lesion. *(V.V.I. for VIVA in Medicine also)*

Ans.

1 possible complication of percutaneous needle biopsy of lung lesion: Iiatrogenic pneumothorax.

(Ref: Davidson's/23rd/601)

Nice to Know:

Treatment options for different lung cancers: SCLCs are best treated with *chemotherapy*, because almost all are **metastatic at presentation**. The other carcinomas may be **curable by surgery** if **limited to the lung. Targeted therapies**, such as **EGFR inhibitor therapy** for **adenocarcinomas** with EGFR mutations, can be effective.

(Ref: Robbins BASIC PATHOLOGY/10th/543)

Q. What's the prognosis of lung cancer? *(For VIVA)*

Ans.

Prognosis of lung cancer: Poor (no effective screening method) - 5 year survival rate is 15%.

Small cell carcinoma has the ***worst prognosis*** since surgical treatment is ineffective though the tumour is sensitive to radiotherapy and chemotherapy.

(Ref: Pathoma Lecture Notes; Harsh Mohan/7th/483)

Q. A 55 years old smoker has multiple centrally located mass on chest X-ray. He also has increasing left shoulder pain. On examination hard enlarged left cervical lymph node was found. What is the most likely diagnosis? How will you further investigate the patient? (RU-'4Ju)

Ans.

Probable diagnosis: Bronchogenic carcinoma with metastasis to left cervical lymph node.

{***Note:*** *Peak incidence of bronchogenic carcinoma is in 50s and 60s. This occurs much more commonly in smoker.*}

Other investigations:

1. **To confirm the diagnosis:**
   - **Bronchoscopy and biopsy** followed by histopathology & immunohistochemistry (if needed)
   - **Sputum cytology for malignant cells** (exfoliative cytology)
   - **FNAC (or biopsy)** of left cervical lymph node.
2. **To see the evidence of metastasis** (for staging purpose):
   - USG of whole abdomen
   - CT scan of chest, abdomen and pelvis
   - Whole body isotope bone scan
   - MRI of brain
   - PET-CT scan
3. **Other (base line investigations):**
   - CBC
   - Liver function test (LFT), renal function test (RFT)
   - Pulmonary function test specially FEV_1.

(Ref: Davidson's/23rd/601; Prof. ABM Abdullah/Long Cases in CLINICAL MEDICINE/117)

Q. A male of 50 years has complaints of cough and hemoptysis. His chest X-ray shows an opacity. On clinical examination a hard supraclavicular lymph node was detected. What is the probable diagnosis? Name 3 tests that can help in diagnosis. (DU-12Ja)

Ans.

Probable diagnosis: Bronchogenic carcinoma with metastasis to supraclavicular lymph node.

3 tests that can help in diagnosis:

- **Bronchoscopy and biopsy** followed by histopathology (if the opacity is central)
- **Image** (CT / USG) **guided core needle biopsy** followed by histopathology (if the opacity is peripheral)
- **FNAC (or biopsy)** of supraclavicular lymph node.

Q. A 75 years old male complaining of chest pain and cough for four months. Repeated x-ray chest was done which reveal progressive increasing opacity in right lung. It was not responding to antibiotic therapy. Last one month noticed a nodular swelling in the right supraclavicular region. What is the probable diagnosis? What other investigations you should do?

Ans.

Probable diagnosis: Bronchogenic carcinoma with metastasis to right supraclavicular lymph node.

*{**Note:** Peak incidence of bronchogenic carcinoma is in 50s and 60s. This occurs much more commonly in smoker. Cough, hemoptysis, breathlessness and chest pain are most common symptoms.}*

Other investigations: *Please write from above.*

Q. A male of 67 years presented with profuse hemoptysis. He has got history of cigarette smoking for last 20 years. How will you proceed to diagnose the case?

Ans.

Probable diagnosis: Bronchogenic carcinoma.

Investigations for diagnosis: *Please write from above.*

Q. An elderly man with history of heavy smoking has presented with cough and haemoptysis. His chest skiagram shows a left hilar shadow. What is the likely diagnosis?

Ans.

Diagnosis: Bronchogenic carcinoma.

Q. Short note: Pancoast tumour. (RU-13Ja)

Ans.

Pancoast tumour: A Pancoast tumor, also called a ***pulmonary sulcus tumor*** or ***superior sulcus tumor***, is a tumor of the pulmonary apex. It is a type of lung cancer defined primarily by its location situated at the top end of either the right or left lung.

It typically spreads to nearby tissues such as the ribs and vertebrae. Most Pancoast tumors are non-small cell cancers.

The growing tumor can cause compression of a brachiocephalic vein, subclavian artery, phrenic nerve, recurrent laryngeal nerve, vagus nerve, or, characteristically, compression of a ***sympathetic ganglion*** resulting in a range of symptoms known as **Horner's syndrome**.

Symptoms:

1. Due to compression of **cervical sympathetic plexus / sympathetic ganglion:** ***Horner's syndrome*** (ipsilateral partial ptosis, miosis, anhidrosis and enophthalmos).
2. Due to compression of **brachial plexus** (in progressive cases)**:** ***Thoracic outlet syndrome*** (pain and weakness in the muscles of the arm and hand)
3. Due to compression of **recurrent laryngeal nerve:** ***Hoarseness of voice*** and bovine cough.

(Ref: Robbins BASIC PATHOLOGY/10th/540 + 10th/721)

The Pleura

Q. Define pleural effusion. Mention its causes.
Q. Short note: Pleural effusion.
Ans.
Pleura effusion: Abnormal accumulation of fluid within pleural space is called pleural effusion.

Pleural fluid normally present: 5 to 15 mL which is serous, relatively acellular, clear fluid.

It is a common manifestation of both ***primary*** and ***secondary pleural diseases***, which may be ***inflammatory*** or ***non-inflammatory***.

Types of pleural effusion with causes:

Conditions	Type of fluid	Cause/example
Inflammatory	Serofibrinous (exudate) Suppurative (pus) Haemorrhagic (bloody exudate)	▪ Pulmonary tuberculosis ▪ Pneumonia ▪ Bronchial carcinoma ▪ Pulmonary infarction ▪ Lymphoma ▪ Collagen disease (SLE, rheumatoid arthritis) ▪ Lung abscess ▪ Bronchiectasis ▪ Pleural mesothelioma ▪ Metastatic involvement of the pleura / Secondaries in the pleura
Non-inflammatory	Hydrothorax (transudate) Haemothorax (blood) Chylothorax (chyle/lymph)	▪ Congestive cardiac failure (CCF) ▪ Nephrotic syndrome ▪ Cirrhosis of liver ▪ Malnutrition ▪ Hypothyroidism ▪ Filariasis ▪ Malignancies that obstruct the major lymphatic ducts (e.g. mediastinal carcinomatosis)

(Ref: Robbins/10th/725)

Nice to Know: ***(For VIVA)***

- **Hydrothorax:** Non-inflammatory collections of ***serous fluid*** within the pleural cavities are called hydrothorax.
- **Haemothorax:** The escape of ***blood*** into the pleural cavity is known as hemothorax.
- **Chylothorax:** Chylothorax is an accumulation of ***milky fluid***, usually of ***lymphatic origin***, in the pleural cavity.
- **Empyema:** Accumulation of ***pus*** in pleural space.

(Ref: Robbins/10th/725; Lecture SSMC & DMC)

Q. Mention the common causes of pleural effusion. (CU-19Nv)

Ans.

Common causes of pleural effusion:

Types	Common causes
Exudative (protein >3 gm%):	▪ Pulmonary tuberculosis ▪ Pneumonia ▪ Bronchial carcinoma ▪ Pulmonary infarction ▪ Collagen disease (SLE, rheumatoid arthritis) ▪ Lymphoma ▪ Pleural mesothelioma ▪ Secondaries in the pleura
Transudative (protein <3 gm%):	▪ Congestive cardiac failure (CCF) ▪ Nephrotic syndrome ▪ Cirrhosis of liver ▪ Malnutrition ▪ Hypothyroidism. ▪ Meig's syndrome

Q. What are the most common causes of pleural effusion? (V.V.I. for VIVA)

Ans.

Most common 4 causes of pleural effusion:

1. Pulmonary tuberculosis
2. Pneumonia
3. Bronchial carcinoma
4. Pulmonary infarction.

Q. Short note: Pneumothorax.

Ans.

Pneumothorax: Pneumothorax refers to **air or gas in the pleural cavities,** and may be spontaneous, traumatic, or therapeutic.

Types of pneumothorax:

1. **Spontaneous:** Any form of pulmonary disease that causes rupture of alveoli.
   - Open pneumothorax
   - Closed pneumothorax
   - Tension pneumothorax
2. **Traumatic:** Penetrating chest injury, thoracic surgery.
3. **Therapeutic / Iatrogenic:** During aspiration of pleural fluid.
4. **Idiopathic** in many cases.

Most common causes of pneumothorax:

1. Emphysema
2. Asthma
3. Tuberculosis.

(Ref: Robbins/10th/725)

Nice to Know:

Tension pneumothorax: In this situation, the defect in the alveoli acts as a flap valve and permits the entrance of air during inspiration but fails to permit its escape during expiration. It effective acts as a pump that creates the progressively increasing pressures of tension pneumothorax, which may be sufficient to compress the vital mediastinal structures and the contralateral lung.

(Ref: Robbins/10th/726)

Q. What are the pleural tumours?

Ans.

Pleural tumors:

(a) Primary tumours (tumours arising from pleura):

- ***Benign mesothelioma*** (fibroma)
- ***Malignant mesothelioma*** (with heavy exposure to asbestos).

(b) Secondary / metastatic tumours (most frequently from lung and breast).

(Ref: Robbins/10th/726)

CHAPTER 05

HEAD, NECK AND ORAL CAVITY

Diseases of Head & Neck

Q. What are the causes of midline neck swelling?
Ans.

Causes of midline neck swelling:

1. Submental lymph node
2. Sublingual dermoid cyst
3. Ranula
4. Subhyoid bursa
5. Thyroglossal cyst
6. Ca larynx/ trachea/ oesophagus
7. Thyroid swelling
8. Goitre of the thyroid isthmus
9. Lymph node in suprasternal 'space of burns'
10. Any skin or subcutaneous swelling in neck occupying midline as sebaceous cyst, skin wart, any skin lesion such as SCC, basal cell carcinoma.

Q. Mention 5 causes of unilateral neck swelling?
Ans.

5 causes of unilateral neck swelling:

1. Enlarged lymph node
2. Thyroid swelling
3. Enlargement of submandibular salivary gland
4. Cystic hygroma
5. Branchial cyst
6. Sternomastoid tumor
7. Cervical rib.

Q. Name some cystic swelling in the neck.
Ans.

Cystic swellings in the neck:

1. Thyroglossal cyst
2. Sublingual dermoid cyst
3. Ranula
4. Subhyoid bursa
5. Branchial cyst
6. Laryngocele
7. Cystic hygroma
8. Pharyngeal pouch.

Q. A 12 years old child having localized swelling in the cervical region of the neck. Write the possible causes and how you will investigate for diagnosis? (CU-16Ja,13Ju)

Ans.

Possible causes of neck swelling:

1. Lymph node enlargement
2. Thyroid swelling
3. Sub-mandibular salivary gland tumour
4. Branchial cyst
5. Carotid artery aneurysm

Relevant investigations:

1. Blood for TC, DC, ESR & Hb%
2. If lymph node enlargement → FNAC & biopsy of lymph node
3. If thyroid swelling → Thyroid function test, USG, FNAC & biopy
4. If salivary gland tumour → FNAC & biopsy
5. If branchial cyst → Ultrasonogram
6. Colour Doppler study of carotid vessels.

Q. A female aged 20 years came to you with a. What are the causes of neck swelling and how you are going to investigate the case? (RMU-21Nv,13Ju)

Ans.

Causes of neck swelling that moves with deglutition:

1. Goitre
2. Thyroglossal cyst
3. Sublingual dermoid
4. Thyroid malignancy

Investigations:

1. Thyroid function tests
2. Ultrasonogram of the thyroid including neck
3. Thyroid scan
4. FNAC or biopsy from the swelling
5. Imaging – CT/MRI scan of neck.

Diseases of Oral Cavity

Q. What are the diseases of oral cavity?
Q. What are the common infections of oral cavity?
Ans.
Diseases of oral cavity:

1. **Diseases of teeth and supporting structures:**
   - Caries (tooth decay)
   - Gingivitis
   - Periodontitis
2. **Inflammatory / reactive lesions:**
   - Aphthous ulcer (canker sores)
   - Fibrous proliferative lesions
     - *Irritation fibroma / traumatic fibroma / focal fibrous hyperplasia*
     - *Pyogenic granuloma*
     - *Peripheral ossifying fibroma*
     - *Peripheral giant cell granuloma*
3. **Infections:**
   - Herpes simplex virus infections
   - Other viral infections: Herpes zoster, EBV, cytomegalovirus, enterovirus, and rubeola (measles)
   - Oral candidiasis (thrush)
   - Deep fungal infections: Histoplasmosis, blastomycosis, coccidioidomycosis, cryptococcosis, zygomycosis, and aspergillosis
4. **Oral manifestations of systemic disease** (Hairy leukoplakia)
5. **Precancerous and cancerous lesions:** ***(For VIVA)***
   - Leukoplakia
   - Erythroplakia
   - Squamous cell carcinoma (SCC).
6. **Odontogenic cysts and tumors.**

(Ref: Robbins/10th/731-737)

Q. What is glossitis? Where does it occur?
Ans.
Glossitis: Glossitis implies ***inflammation of the tongue.*** It is sometime applied to the beefy-red tongue encountered in certain deficiency states.

- Deficiency of vitamin B_{12} (pernicious anemia)
- Deficiency of riboflavin, niacin, or pyridoxine
- Deficiency of iron (iron deficiency anemia).

(Ref: Robbins/8th/742)

Q. What is aphthous ulcer? ***(Important for VIVA)***
Ans.
Aphthous ulcer: Aphthous ulcers (canker sores) are **common**, often **recurrent & painful, superficial oral mucosal ulcerations** of unknown etiology.

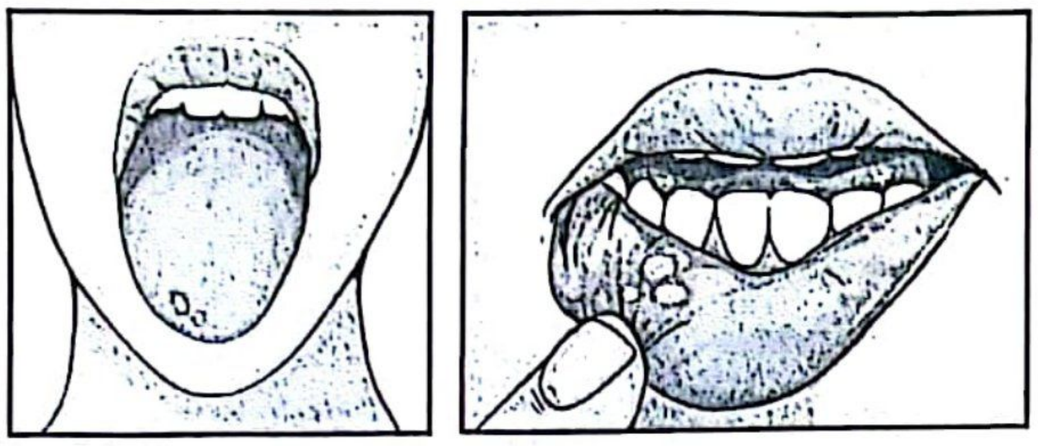


Fig: Aphthous ulcer.

Characteristics of aphthous ulcer:

- They affect up to **40% of the population,** and are most common in the **first two decades of life.**
- Extremely **painful** and **often recurrent.**
- They may be associated with **immunologic disorders** including celiac disease, inflammatory bowel disease, and Behçet disease.
- The lesions appear as **single** or **multiple, shallow, hyperemic,** mucosal ulceration covered by a thin exudate and rimmed by a narrow zone of erythema.
- Lesions typically **resolve spontaneously in 7 to 10 days** but **sometimes persist for weeks,** particularly in immunocompromised patients.

(Ref: Robbins/10th/732)

Q. What are the tumours and precancerous lesions of oral cavity?

Ans.

Tumours and precancerous lesions of oral cavity: ***(For VIVA)***

1. Leukoplakia
2. Erythroplakia
3. Squamous cell carcinoma (SCC).

(Ref: Robbins/10th/731,734)

Q. What is leukoplakia? (CU-19/18Nv) **State its common sites and its pathology.**

Q. Short note: Leukoplakia. (DU-03M) ***(For VIVA)***

Ans.

Leukoplakia: Leukoplakia is defined by the WHO as "a white patch or plaque that cannot be scraped off and cannot be characterized clinically or pathologically as any other disease."

Until proven otherwise by means of histologic evaluation, all leukoplakias must be considered **precancerous.**

Age at incidence: Adults at any age, but they are usually found in persons 40 to 70 years of age, with a 2 : 1 male preponderance.

Cause: *Multifactorial origin*, but most important cause is the **use of tobacco** (cigarettes, pipes, cigars and certain forms of smokeless tobacco).

Sites: May occur ***anywhere in the oral cavity***. But the favoured sites are-

- Buccal mucosa
- Floor of the mouth
- Ventral surface of tongue, palate and gingiva.

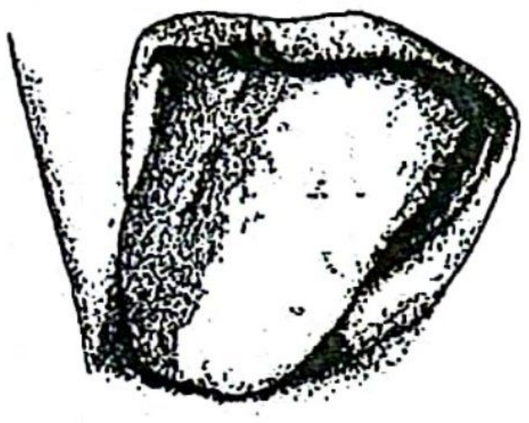


Fig: Leukoplakia.

Morphology:

Macroscopic:

- Solitary or multiple white patches or plaques.
- Sharply demarcated borders.
- They may be slightly thickened and smooth or wrinkled and fissured, or they may appear as raised, sometimes corrugated, verrucous plaques.

Microscopic: Spectrum of epithelial changes ranging from-

- Hyperkeratosis overlying a thickened, acanthotic but orderly mucosal epithelium *to*
- Lesions with markedly dysplastic changes sometimes merging into carcinoma in situ.

Clinical importance: It is a **precancerous state**. So, it may turn into malignancy {**squamous cell carcinoma (SCC)**}.

(Ref: Robbins/10th/734)

Q. What is erythroplakia? (CU-18Nv)

Q. Short note: Erythroplakia. ***(For VIVA)***

Ans.

Erythroplakia: Erythroplakia is a red, velvety, possibly eroded area within the oral cavity that usually remains level with or may be slightly depressed in relation to the surrounding mucosa.

The epithelium in such lesions tends to be markedly atypical, incurring a much higher risk of malignant transformation (**pre-malignant**).

Age at incidence: Adults at any age, but they are usually found in persons 40 to 70 years of age, with a 2 : 1 male preponderance.

Cause: *Multifactorial origin*, but most important cause is the **use of tobacco** (cigarettes, pipes, cigars and certain forms of smokeless tobacco).

Histology of erythroplakia:

- Severe dysplasia / carcinoma in situ / minimally invasive carcinoma (approx. 90% cases)
- An intense subepithelial inflammatory reaction with vascular dilatation accounts for the reddish clinical appearance of the lesion.

Clinical importance: It is a **precancerous state**. Risk of **malignant transformation (SCC)** is much higher than is leukoplakia.

(Ref: Robbins/10th/734)

(***N.B*: Intermediate forms** that have the characteristics of both **leukoplakia** and **erythroplakia** are termed ***speckled leukoerythroplakia***.)

(Ref: Robbins/10th/735)

Salivary Gland

Q. Define xerostomia and sialadenitis. ***(For VIVA)***

Ans.

Xerostomia: Xerostomia is defined as a **dry mouth** resulting from a decrease in the production of saliva.

(Ref: Robbins/10th/747)

Sialadenitis: Sialadenitis refers to the **inflammation of the salivary gland** which may be of traumatic, viral, bacterial, or autoimmune origin.

(Ref: Robbins/10th/747,751)

(***N.B:*** The most common viral cause of sialadenitis is **mumps,** which affects the major salivary glands, particularly the **parotids,** and frequently involves other glandular organs such as the **pancreas** and **testes).**

(Ref: Robbins/10th/747)

Q. What is Sjögren syndrome?

Ans.

Sjögren syndrome: Sjögren syndrome is a chronic disease characterized by **dry eyes** (*keratoconjunctivitis sicca*) and **dry mouth** (*xerostomia*) resulting from **immunologically mediated destruction** of the **lacrimal** and **salivary glands**.

(Ref: Robbins/10th/229)

(***N.B:*** It occurs as an isolated disorder (**primary form**), also known as the ***sicca syndrome,*** or more often in association with another autoimmune disease (**secondary form**). Among the associated disorders, rheumatoid arthritis is the most common, but some patients have SLE, polymyositis, scleroderma, vasculitis, mixed connective tissue disease, or thyroiditis.)

(Ref: Robbins/10th/229)

Tumors of Salivary Glands

Q. Classify salivary gland tumours/neoplasms. (RMU-23/22M,10Ju) ***(For VIVA)***
Q. Classify tumors of salivary glands. (RU-19/18M,17Ju/M,15/13/08/06Ja, CU-19M,18Nv,09/07Ja)
Q. Enumerate the malignant neoplasms of salivary gland. (RU-20M)
Q. Short note: Classification of salivary gland tumour. (RU-16Ja)

Ans.

Tumors of salivary glands: The majority of the **salivary gland tumours** occur in the **parotid gland** (65% to 80%). The majority of parotid tumors are **benign**, but 40% of submandibular, 50% of minor salivary gland, and 70% to 90% of sublingual tumors are **malignant**.

Benign tumors:

- Pleomorphic adenoma (mixed tumour) (50%)
- Warthin tumour
- Oncocytoma
- Canalicular adenoma
- Basal cell adenoma
- Other adenomas
- Ductal papillomas

Malignant tumors:

- Mucoepidermoid carcinoma
- Acinic cell carcinoma
- Adenoid cystic carcinoma
- Adenocarcinoma, not otherwise specified
- Carcinoma ex pleomorphic adenoma
- Squamous cell carcinoma
- Other carcinomas.

(Ref: Robbins/10th/748; BRS Pathology/5th/226)

Q. Give the morphologic / histological features of pleomorphic adenoma. (RMU-23/22/21M,06Ja, CMU-23M,19Nv,07Ja)
Q. Give the morphology of pleomorphic adenoma. (RU-18M,13Ja,10Ju, CU-09Ja)
Q. Short note: Pleomorphic adenoma. (DU-04Ja, CMU-21Nv,15Ju, RU-20/19M,07Ju)

Ans.

Pleomorphic adenoma (mixed tumour)**:** Pleomorphic adenoma is a **benign, slow-growing** neoplasm composed of a **heterogenous mixture of epithelial and mesenchymal cells.**

(Ref: Robbins/10th/751)

Pleomorphic adenomas are the **most common salivary gland neoplasms.** They represent about 60% of tumors in the *parotid*, are less common in the *submandibular glands*, and are relatively rare in the *minor salivary glands*.

Cause: Is little known, but **radiation exposure** increase the risk.

Characteristics:

- Pleomorphic adenomas are **benign tumors** that consist of a **mixture of ductal (epithelial), myoepithelial,** and **mesenchymal cells**, which explains why they are also termed ***mixed tumors***.
- **Malignant transformation is rare**. When they appear, these cancers are among the most aggressive of all salivary gland neoplasms, with mortality rates of 30% to 50% at 5 years
- Cancers are usually **adenocarcinomas** or **undifferentiated carcinomas**.

Clinical features:

1. Painless, slow growing, mobile, discrete masses within the parotid or submendibular areas or in the buccal cavity.
2. Often, the tumour is difficult to remove completely because of its proximity to the facial nerve, and it is likely to recur after resection.
3. The rate of recurrence following parotidectomy is about 4%.

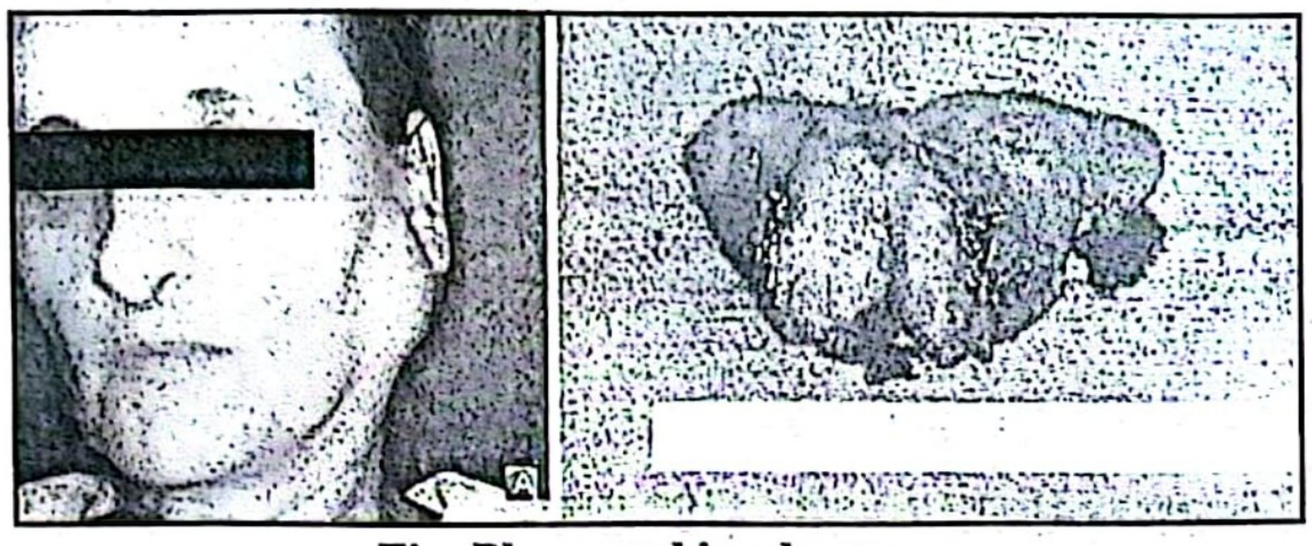


Fig: Pleomorphic adenoma.

Morphology:

Macroscopic:

- Rounded, **well demarcated** masses that rarely exceed 6 cm in greatest dimension.
- They are **encapsulated** with some exceptions e.g. in palate, where the capsule is not fully developed.
- Cut surface is **gray-white** with **myxoid** and **blue translucent** areas of **chondroid (cartilage-like) stroma**.

Microscopic / Histologic:

- Great heterogeneity.
- The epithelial elements resembling **ductal cells** or **myoepithelial cells** are arranged as ducts, acini, irregular tubules, strands, or sheets of cells.
- These elements are typically **dispersed within** a background of loose **myxoid** and **hyaline tissue** containing **island of cartilage** and, rarely, **foci of bone**.

(Ref: Robbins/10th/748; BRS Pathology/5th/226)

Q. Why it is called pleomorphic adenoma? (RU-18M)

Ans.

Naming of pleomorphic adenoma: Pleomorphism is a term used in histology and cytopathology to describe ***variability in the size, shape and staining of cells and/or their nuclei***. An **adenoma** is a ***benign tumor*** originating in ***glandular tissue***.

Pleomorphic adenoma consists of a **mixture** of **ductal (epithelial), myoepithelial** and **mesenchymal cells**, and therefore it shows both ***epithelial*** and ***mesenchymal*** {myxoid & chondroid (cartilage-like) elements} differentiation. Because of this ***remarkable histologic diversity***, this adenoma is called **"Pleomorphic adenoma"**.

(Ref: Robbins/10th/748; BRS Pathology/5th/226; Lecture DMC)

Q. Give the morphologic features of adenoid cystic carcinoma. (RU-03Ja)

Ans.

Adenoid cystic carcinoma: It is a relatively **uncommon tumor**, which in approximately 50% of cases is found in the **minor salivary glands** (in particular the **palatine glands**). Among the major salivary glands, the parotid and submandibular glands are the most common locations.

(Ref: Robbins/10th/751)

Morphologic features of adenoid cystic carcinoma:

***Gross appearance*:**

1. They are generally small, poorly encapsulated, infiltrative, gray-pink lesions.

***Microscopic*:**

1. They are composed of small cells having dark, compact nuclei and scant cytoplasm.
2. The tumor cells are organized in a cribriform growth pattern that resembles swiss cheese.
3. The spaces between the tumor cells are often filled with hyaline material thought to represent excess basement membrane.
4. Less common histologic patterns are tubular and solid.

(Ref: Robbins/10th/751)

Nose & Nasopharynx

Q. Name the tumours of nose, sinuses & nasopharynx.

Ans.

Tumours of nose, sinuses & nasopharynx:

- Nasopharyngeal angiofibroma
- Sinonasal (Schneiderian) papilloma
- Olfactory neuroblastoma (Esthesioneuroblastoma)
- NUT midline carcinoma
- Nasopharyngeal carcinoma (associated with EBV infection).

(Ref: Robbins/10th/741)

CHAPTER 06

GASTROINTESTINAL TRACT

Esophagus

Q. Name the pathological conditions /diseases of esophagus.
Q. What are the congenital anomalies of esophagus? (CMU-23M)
Ans.
Diseases of esophagus:

1. **Congenital anomalies:** ***(Important for VIVA)***
   - Agenesis (*congenital absence of oesophagus*)
   - Stenosis (*lumen is markedly reduced in caliber as a result of fibrous thickening of the wall*)
   - Atresia (*segment of esophagus is non-canalized*)
   - Fistula (*tracheo-esophageal fistula*)
   - Esophageal mucosal webs (*thin protrusion of esophageal mucosa*)
   - Esophageal rings (or *Schatzki rings*)
2. **Motor dysfunction:**
   - Achalasia
   - Diverticula
   - Hiatus hernia
3. **Esophagitis:**
   - Lacerations *(Mallory-Weiss tear)*
   - Chemical and infectious oesophagitis *(e.g. alcohol, corrosive acids or alkalis)*
   - Reflux oesophagitis / gastroesophageal reflux disease (GERD)
   - Eosinophilic oesophagitis *(atopic)*
4. **Esophageal varices** *(an important cause of esophageal bleeding)*
5. **Barrett oesophagus** *(complication of chronic GERD that is characterized by intestinal metaplasia within the esophageal squamous mucosa)*
6. **Esophageal tumors:**
   - **A. Benign:**
     - **Epithelial:**
       - Squamous cell papilloma

- Condyloma

- **Mesenchymal:**
  - **Leiomyoma**
  - Lipoma
  - Fibroma
  - Neurofibroma
  - Rhabdomyoma
  - Haemangioma
  - Lymphangioma

B. Malignant: *(Important for VIVA)*

- **Squamous cell carcinoma**
- **Adenocarcinoma**
- Undifferentiated carcinoma
- Carcinoid tumor
- Melanoma
- Lymphoma
- Sarcoma.

(Ref: Robbins/10th/753-764)

Q. Mention the esophageal causes of hematemesis.

Ans.

Esophageal causes of hematemesis:

- Lacerations (Mallory-Weiss syndrome)
- Esophageal perforation (cancer or Boerhaave syndrome)
- Varices (cirrhosis)
- Esophageal-aortic fistula (usually with cancer)
- Chemical and pill esophagitis
- Infectious esophagitis (*Candida,* herpes)
- Benign strictures
- Vasculitis (autoimmune, cytomegalovirus)
- Reflux esophagitis (erosive)
- Eosinophilic esophagitis
- Esophageal ulcers (many etiologies)
- Barrett esophagus
- Adenocarcinoma
- Squamous cell carcinoma
- Hiatal hernia.

(Ref: Robbins/10th/758)

Q. What are the causes of esophageal obstruction?

Ans.

Causes of esophageal obstruction:

1. Esophageal webs, rings, stenosis
2. Esophageal dysmotility
   - Nutcracker esophagus
   - Diffuse esophageal spasm
   - Lower esophageal sphincter dysfunction
3. Diverticula
   - Zenker (*pharyngoesophageal*) diverticula
   - Traction diverticulum
   - Epiphrenic diverticulum.

(Ref: Robbins/10th/757)

Nice to Know: ***(Important for VIVA)***

Paterson-Brown-Kelly or ***Plummer-Vinson syndrome*** is characterized by **esophageal web** accompanied by **severe iron-deficiency anemia, glossitis,** and **cheilosis.**

(Ref: Robbins/10th/757)

Q. Short note: Achalasia. *(Important for VIVA)*

Ans.

Achalasia: Disordered esophageal motility with inability to relax the lower esophageal sphincter (LES).

Or,

Achalasia is persistent contraction of the lower esophageal sphincter and absence of esophageal peristalsis, leading to dilation of the esophagus.

Or,

It is a neuromuscular dysfunction of the oesophagus due to which the cardiac sphincter fails to relax during swallowing and results in progressive dysphagia and dilatation of the oesophagus ***(mega-oesophagus).***

Achalasia is characterized by the **triad** of-

- Incomplete lower esophageal sphincter relaxation
- Increased lower esophageal sphincter tone
- Aperistalsis of the esophagus.

Types & causes of achalasia:

1. **Primary achalasia:** It is rare and results from **degeneration of nitric oxide–producing neurons** that normally induce lower esophageal sphincter relaxation. Degenerative changes in the ***extraesophageal vagus nerve*** or the ***dorsal motor nucleus of the vagus*** may also occur.
2. **Secondary achalasia:** It may arise in **Chagas disease,** in which *Trypanosoma cruzi* infection causes destruction of the myenteric plexus, failure of peristalsis, and esophageal dilation.

Clinical features:

1. Dysphagia (difficulty in swallowing) for solids and liquids
2. Putrid breath
3. High LES pressure on esophageal manometry
4. 'Bird-beak' sign on barium swallow study
5. Increased risk of esophageal squamous cell carcinoma

Treatment: Treatments for both primary and secondary achalasia aim to overcome the obstruction and include-

- Laparoscopic myotomy
- Pneumatic balloon dilatation
- Botulinum neurotixin (Botox) injection (to inhibit contraction-promoting cholinergic neurons).

(Ref: Robbins/10th/757; BRS Pathology/5th/228; Pathoma/2014/102; Harsh Mohan/7th/521)

Q. What is oesophagitis? Give some examples.

Ans.

Oesophagitis: Inflammation of the **oesophageal mucosa** is known as **oesophagitis.**

Examples:

a. Lacerations *(Mallory-Weiss tear)*
b. Chemical and infectious oesophagitis *(e.g. by alcohol, corrosive acids or alkalis, excessive hot fluids, heavy smoking, radiation therapy etc.)*
c. Reflux oesophagitis / gastroesophageal reflux disease (GERD)
d. Eosinophilic oesophagitis *(atopic)*

(Ref: Robbins/10th/758)

Q. What is Malloy-Weiss syndrome? *(Important for VIVA)*

Ans.

Malloy-Weiss syndrome: Longitudinal mucosal tears near the **gastroesophageal junction** are termed *Mallory-Weiss tears,* and are most often associated with **severe retching** or **vomiting** secondary to **acute alcohol intoxication.**

The patient presents with **painful hematemesis.**

(Ref: Robbins/10th/758)

Q. Short note: Reflux oesophagitis / GERD. *(Important for VIVA)*

Ans.

Reflux esophagitis: Reflux of **gastric acid** into the **lower esophagus** due to **reduced lower esophageal sphincter tone** is termed as ***gastro-esophageal reflux disease (GERD)***.

Or,

GERD is the **reflux of gastric contents** into the **lower esophagus**.

{***N.B:*** It is the **opposite of achalasia**, where **LES** (lower esophageal sphincter) **tone is increased**}.

Causes: Conditions that **decrease LES tone** or **increase abdominal pressure** contribute to GERD:

1. **Transient lower esophageal sphincter relaxation** (mediated via vagal pathways)
2. **Abrupt increases in intra-abdominal pressure** (e.g. after coughing, straining, or bending)
3. **Other conditions that are associated with GERD include:**
   - Alcohol and tobacco use
   - Obesity
   - Fat-rich diet
   - Caffeine
   - Centralnervous system depressants
   - Pregnancy
   - Hiatal hernia
   - Delayed gastric emptying
   - Increased gastric volume.

Clinical features of GERD: Typical symptoms include-

1. Heartburn (mimics cardiac chest pain, which may be mistaken for ischemic heart disease)
2. Dysphagia
3. Regurgitation of sour-tasting gastric contents (most often postprandially)
4. Asthma (adult-onset) and cough
5. Damage to enamel of teeth.

Treatment: Proton pump inhibitors (PPIs).

Complications:

1. Esophagitis
2. Esophageal ulceration with stricture
3. Barrett esophagus (columnar metaplasia of esophageal squamous epithelium).

Histology:

1. **Mild GERD:** Simple **hyperemia,** evidenced by **redness.**
2. **More significant gastric reflux** is associated with **erosions** and **influx of eosinophils** into the squamous mucosa. **Basal zone hyperplasia** and **elongation of lamina propria papillae** are also common. Neutrophil infiltration is less frequent and is generally associated with bacterial or fungal infection or chemical damage.

(Ref: Robbins/10th/759; BRS Pathology/5th/228; Pathoma/2014/102)

Q. Short note: Hiatal hernia.

Ans.

Hiatal hernia: Hiatus hernia is the herniation or protrusion of part of the stomach through the oesophageal hiatus of the diaphragm.

It may cause lower esophageal sphincter incompetence and symptoms that are similar to GERD but it is symptomatic in fewer than 10% of adults.

Anatomical types: There are 3 patterns in hiatus hernia-

1. **Sliding or oesophago-gastric hernia** (most common, occurring in 85% of cases): The herniated part of the stomach appears as supra-diaphragmatic bell due to sliding up on both sides of the oesophagus.
2. **Rolling or para-oesophageal hernia** (10% of cases): This is a true hernia in which cardiac end of the stomach rolls up para-oesophageally, producing an intrathoracic sac.
3. **Mixed or transitional hernia** constitutes the remaining 5% cases in which there is combination of sliding and rolling hiatus hernia.

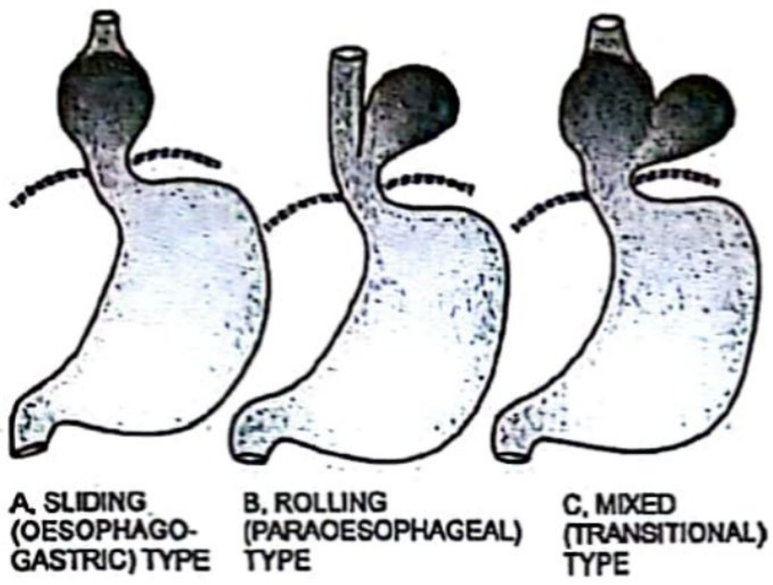


Fig: Patterns of hiatus hernia.

Clinical features:

- Heartburn (retrosternal burning sensation)
- Regurgitation of gastric juice into the mouth.

Both of above features are worsened due to heavy work, lifting weights and excessive bending.

Complication of hiatal hernia:

- Ulceration
- Bleeding
- Perforation
- Reflux esophagitis (more associated with sliding hernias).

(Ref: Robbins/10th/760; Harsh Mohan/7th/521)

Q. What is esophageal varices? Mention its mechanism. *(Important for VIVA)*

Ans.

Oesophageal varices: Esophageal varices are **dilated veins** within the **lower esophagus.**

(Ref: Robbins/10th/760)

Or,

Esophageal varices are **tortuous dilated veins** lying primarily within the **mucosa & submucosa** of the **distal esophagus** and **proximal stomach;** that occur **secondary to portal hypertension** can result in **upper gastrointestinal hemorrhage.**

It develops in 90% of ***cirrhotic patients***, most commonly in association with ***alcoholic liver disease.***

Clinical features: Mostly **asymptomatic,** but risk of **rupture** exists. **Variceal rupture** results in **hemorrhage** into the lumen or the esophageal wall. Patients present with **painless hematemesis.** It is the ***most common cause of death in cirrhosis.***

Morphology /pathology:

***Macroscopic features*:**

- A red, velvety mucosa located between smooth, pale pink esophageal squamous mucosa and light-brown gastric mucosa
- It may exist as tongues or patches (islands).

***Microscopic features*:**

- The most common finding is the replacement of squamous epithelium by metaplastic columnar cells, along with goblet cells *(definitive diagnosis)*
- Intestinal metaplasia may be accompanied by dysplastic changes of the columnar epithelium or glands (ranging from low to high grade)
- Inflammatory changes, acute or chronic, are commonly accompanied.

Diagnosis: 2 criteria are required for diagnosis of Barret esophagus-

- **Endoscopic evidence** of ***metaplastic columnar mucosa*** above the gastroesophageal junction
- **Histologic evidence** of ***intestinal-type metaplasia*** in biopsy specimen showing replacement of the squamous esophageal epithelium with ***goblet cells***.

Reatment options:

- Surgical resection
- Esophagectomy
- Newer modalities such as photodynamic therapy, laser ablation, and endoscopic mucosectomy
- Follow-up with endoscopy and biopsy at regular intervals.

Complications:

1. Local ulceration with bleeding and stricture.
2. Esophageal adenocarcinoma.

(Ref: Robbins/10th/761; Harsh Mohan/7th/523)

Q. Mention the diagnostic criteria of Barrett esophagus.

Ans.

Diagnostic criteria of Barrett esophagus: Two criteria are required for the diagnosis of Barrett esophagus-

1. **Endoscopic evidence** of metaplastic columnar mucosa above the gastroesophageal junction
2. **Histologic evidence** of intestinal-type metaplasia in biopsy specimen showing replacement of the squamous esophageal epithelium with goblet cells.

(***N.B*: Goblet cells** are **diagnostic of Barrett esophagus** and have distinct mucous vacuoles that stain pale blue and impart the shape of a wine goblet to the remaining cytoplasm).

(Ref: Robbins/10th/761)

Nice to Know:

Esophageal adenocarcinoma: Esophageal adenocarcinoma typically arises in the background of **Barrett esophagus** and **long-standing GERD**.

Thus, increased rates of esophageal adenocarcinoma may be partly due to the increased incidence of **obesity-related gastroesophageal reflux** and **associated Barrett esophagus**. Other major **risk factors** include tobacco use and exposure to radiation.

Conversely, **risk is reduced** by diets rich in fresh fruits and vegetables. Some serotypes of *Helicobacter pylori* are associated with decreased risk of esophageal adenocarcinoma, perhaps because they cause gastric atrophy, which decreases acid secretion and reduces reflux-induced esophageal damage.

Clinical features: Although esophageal adenocarcinomas are occasionally discovered incidentally during the evaluation of GERD or surveillance of Barrett esophagus; they more commonly present with:

Mechanism of oesophageal varices: Esophageal varices are caused by portal hypertension, which is duc to impaired blood flow through the portal venous system and liver.

Liver cirrhosis
↓
Fibrosis of liver
↓
Obstruction of the flow of blood from gastrointestinal tract in the portal system
↓
Portal hypertension
↓
Porto-systemic shunting
↓
Anastomotic channels connecting the portal and systemic venous systems open up and become distended
↓
Esophageal varices.

(Ref: Robbins/10th/760; BRS Pathology/5th/228; Pathoma/2014/101)

Q. What is Barrett esophagus? (CU-19M) **Mention its clinical importance.** (DU-08Ju)
Q. Explain Barrett's esophagus. (CU-18Nv)
Q. Short note: Barrett esophagus. (DU-06S/Ja, CMU-21Nv,20M) ***(Important for VIVA)***
Ans.
Barrett esophagus: Barrett esophagus is a **long-standing complication** of **chronic gastro-esophageal reflux disease (GERD)** that is characterized by **intestinal metaplasia** within the **esophageal squamous mucosa** and is associated with an **increased risk of cancer**.

It is the single most important risk factors for **esophageal adenocarcinoma**.

Incidence: It is estimated to occur in as many as **10% of individuals with symptomatic GERD**. Peak age is 40-60 years of age.

Pathogenesis: In Barrett esophagus, the ***distal squamous epithelium is replaced by metastatic columner epithelium*** as a response to prolonged injury.

Barrett's oesophagus is a **premalignant condition** evolving sequentially-from **Barrett's epithelium** (columnar metaplasia with goblet cells) to **dysplasia** to **carcinoma *in situ*** and finally to **oesophageal adenocarcinoma**.

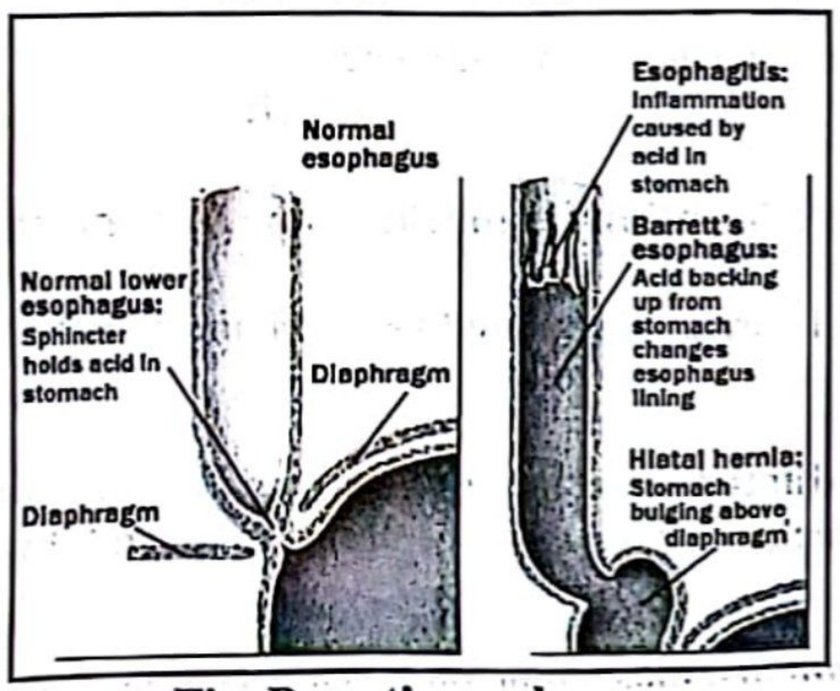

Normal esophagus
Esophagitis: Inflammation caused by acid in stomach
Barrett's esophagus: Acid backing up from stomach changes esophagus lining
Hiatal hernia: Stomach bulging above diaphragm
Normal lower esophagus: Sphincter holds acid in stomach
Diaphragm
Diaphragm

Fig: Barret's esophagus.

- Pain or difficulty in swallowing
- Progressive weight loss
- Hematemesis
- Chest pain
- Vomiting.

By the time symptoms appear, the tumor has often spread to submucosal lymphatic vessels. As a result, overall 5-year survival is less than 25%. In contrast, 5-year survival is approximately 80% in cases in which adenocarcinoma islimited to the mucosa or submucosa.

(Ref: Robbins/10th/762)

Q. Mention the risk factors of esophageal squamous cell carcinoma.
Q. Write down the etiopathogenesis of squamous cell carcinoma of esophagus.
Ans.
Risk factors of esophageal squamous cell carcinoma: Esophageal squamous cell carcinoma occurs in **adults older than age 45** and affects **males four times more frequently than females**. Risk factors include-

1. **Dietary:**
   - Deficiency of vitamins (A, C, B_2, thiamin, B_6)
   - Deficiency of trace elements (Zn, Mo)
   - Deficiency of fruits or vegetables
   - High content of nitrites / nitrosamines
   - Betel chewing
2. **Life style:**
   - **Poverty**
   - Frequent consumption of **very hot beverages**
   - Fungus-contaminated foods
   - **Alcohol** consumption
   - **Tobacco** use
3. **Esophageal disorder:**
   - **Caustic esophageal injury**
   - **Achalasia**
   - **Tylosis**
   - Hiatus hernia
   - Diverticula
   - **Plummer-Vinson syndrome**
4. **Genetic predisposition:**
   - Long standing coeliac disease
   - Ectodermal dysplasia
   - Epidermolysis bullosa
   - Racial disposition (*more common in African American*)
5. **Previous radiation to the mediastinum** (5 to 10 or more years after exposure).

(Ref: Robbins/10th/763,764; Lecture SSMC)

Q. Mention the sites of esophageal cancer. ***(Very Important for VIVA)***
Ans.
Sites of esophageal cancer:

- **Squamous cell carcinoma** arises most frequently in the **upper** and **middle thirds** of the esophagus.
- **Adenocarcinoma** arises most frequently in the **lower third** of the esophagus.

(Ref: Robbins/10th/762,763; BRS Pathology/5th/229; Pathoma/2014/103)

Q. Write down the morphologic patterns of esophageal squamous cell carcinoma.

Ans.

Morphologic patterns of esophageal squamous cell carcinoma: Three morphologic patterns are described-

1. **Protruded (60%):** A ***polypoid***, or ***exophytic*** lesion that **protrudes into** and **obstruct the lumen.**
2. **Flat (15%):** An ***ulcerated*** or ***diffusely infiltrative lesion*** spread within the wall of the esophagus, causing **thickening, rigidity**, and **luminal narrowing.**
3. **Excavated (25%):** Tumors may **invade surrounding structures** including the **respiratory tree** (causing pneumonia), the **aorta** (causing catastrophic exsanguination), or the **mediastinum** and **pericardium.**

(Ref: Robbins/10th/764)

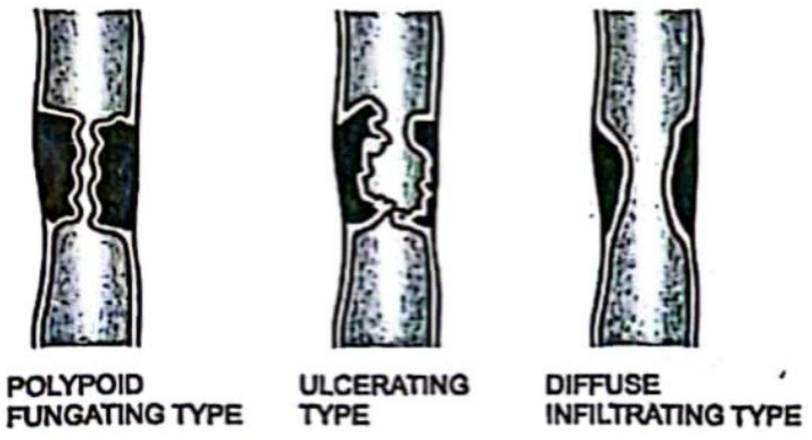


Fig: Morphologic patterns of esophageal carcinoma.

Stomach

NORMAL STRUCTURE:

The stomach is **'gland with cavity'**, extending from its junction with lower end of the oesophagus (cardia) to its junction with the duodenum (pylorus). The ***lesser curvature*** is inner concavity on the right, while the ***greater curvature*** is the outer convexity on the left side of the stomach.

The stomach has 5 anatomical regions:

1. **Cardia** is the oesophagogastric junction and lacks the sphincter.
2. **Fundus** is the portion above the horizontal line drawn across the oesophagogastric junction.
3. **Body** is the middle portion of the stomach between the fundus and the pyloric antrum.
4. **Pyloric antrum** is the distal third of the stomach.
5. **Pylorus** is the junction of distal end of the stomach with the duodenum. It has powerful sphincter muscle.

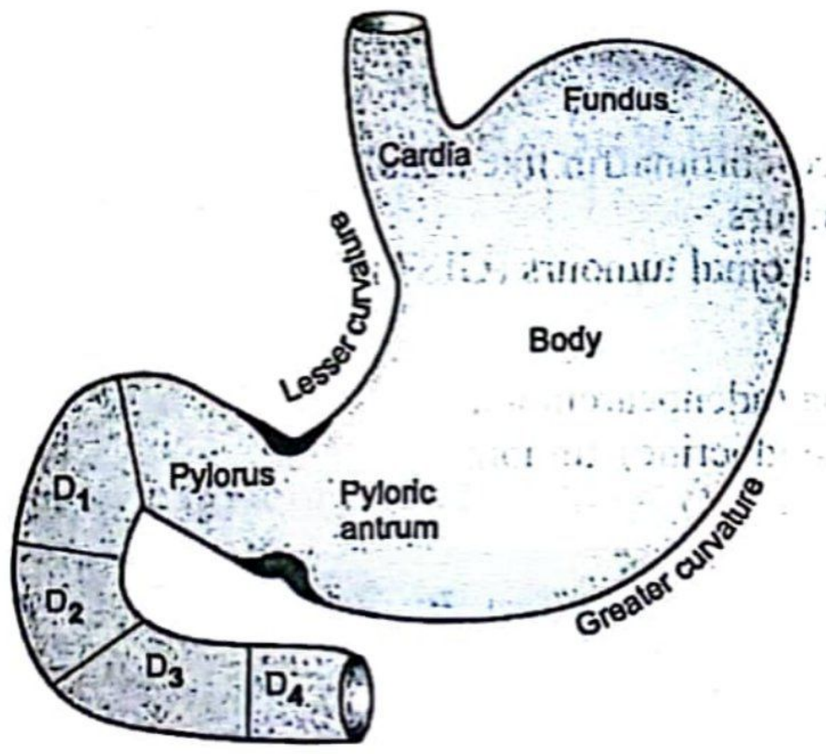


Fig: Anatomical subdivisions of the stomach.

(Ref: Harsh Mohan/7th/526)

Q. Classify diseases of stomach.

Q. What are the common malignant neoplasms of stomach?

Ans.

Diseases of stomach:

1. **Congenital anomalies**
   - Ectopia
   - Diaphragmatic hernia
   - *Congenital hypertrophic pyloric stenosis*
2. **Gastropathy and acute gastritis**
3. **Stress-related mucosal disease**
   - Stress ulcers
   - Curling ulcers
   - Cushing ulcers
4. **Chronic gastritis and its complications**
   - *Helicobacter pylori* gastritis
   - Autoimmune atrophic gastritis
   - Uncommon forms of gastritis
     - *Eosinophilic gastritis*
     - *Lymphocytic gastritis*
     - *Granulomatous gastritis*
   - Peptic ulcer disease (PUD)
   - Other complications of chronic gastritis
     - *Mucosal atrophy and intestinal metaplasia*
     - *Dysplasia*
     - *Gastritis cystica*
5. **Hypertrophic gastropathies**
   - Ménétrier disease
   - Zollinger-Ellison syndrome
6. **Acquired pyloric stenosis**
7. **Gastric polyps and tumours:**
   a. **Benign:**
      - Gastric polyp
        - Inflammatory and hyperplastic polyps
        - Fundic gland polyps
      - Adenoma
      - Leiomyoma
      - Neurofibroma
      - Lipoma
      - Tumours of entero-chromaffin like cells
      - Granular cell tumours
      - Gastrointestinal stromal tumours (GIST)

   b. **Malignant:**
      - Gastric carcinoma (adenocarcinoma)
      - Carcinoid (neuroendocrine) tumors
      - Lymphoma
      - Leiomyosarcoma
      - Schwannoma.

(Ref: Robbins/10th/753,764-779)

***(N.B:** Rarely, **stomach** may be involved in **tuberculosis, sarcoidosis** and **Crohn's disease.**)*

(Ref: Harsh Mohan/7th/529)

Nice to Know:

Pyloric stenosis: Pyloric stenosis may be either **congenital** or **acquired.**

A. **Congenital hypertrophic pyloric stenosis:** It may be defined as **congenital hypertrophy of pyloric smooth muscle** (more common in males).

Anatomically, the gastric outflow tract is obstructed by hyperplasia of the pyloric muscularis propria. Edema and inflammatory changes in the mucosa and submucosa may aggravate the narrowing.

Clinical presentation: Classically presents between the third and sixth weeks of life as-

- New-onset regurgitation
- Projectile non-bilious vomiting after feeding
- Frequent demands for re-feeding
- Visible peristalsis (left-to-right)
- Olive-like mass in the abdomen
- Constipation
- Loss of weight.

Diagnosis: By ultrasonography.

Treatment: Surgical splitting of the muscularis (myotomy).

B. **Acquired pyloric stenosis:** It occurs in adults as a consequence of antral gastritis or peptic ulcers close to the pylorus. Carcinomas of the distal stomach and pancreas may also narrow the pyloric channel due to fibrosis or malignant infiltration.

(Ref: Robbins/10th/755; Pathoma/2014/103; Harsh Mohan/7th/529)

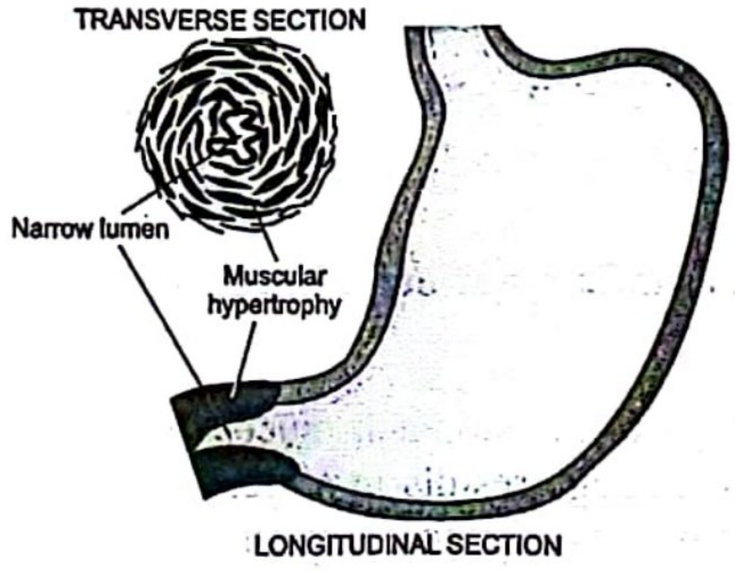


Fig: Congenital hypertrophic pyloric stenosis.

Q. Write down the WHO histological classification of gastric tumours.
Q. Classify the tumours of stomach. (BUP-22M, CU-16Ja)
Q. Classify malignant neoplasms of stomach. (RU-10Ju)
Q. Classify gastric tumours. (SU-16Ja)
Q. Classify gastric carcinoma. (CU-20Nv/Ju/M,12Ja)

Ans.

WHO histological classification of gastric tumours: ***(Important for VIVA)***

Origin	Benign tumours	Malignant tumours
Epithelial	Gastric adenoma	**Gastric adenocarcinoma** (*most common; more than 90% of all gastric cancers*) ▪ Papillary adenocarcinoma ▪ Tubular adenocarcinoma

		▪ Mucinous adenocarcinoma ▪ Signet-ring cell carcinoma ▪ Undifferentiated carcinoma ▪ Adenosquamous carcinoma **Small-cell carcinoma** **Carcinoid tumour**
Non-epithelial / Mesenchymal	Leiomyoma Neurofibroma Lipoma Tumours of entero-chromaffin like cells Granular cell tumours Gastrointestinal stromal tumours (GIST)	Malignant stromal tumours Leiomyosarcoma Kaposi-sarcoma Schwannoma
Others		Lymphoma

(Ref: Robbins/10th/773 + 8th/823)

Q. What are the common malignant tumors of GIT? ***(Very Important for VIVA)***

Ans.

Common malignant tumors of GIT:

1. Gastric carcinoma (adenocarcinoma)
2. Colorectal carcinoma (adenocarcinoma 98%)
3. Malignant lymphoma
4. Carcinoid tumors
5. Malignant stromal cell tumors.

Gastritis

Q. Define gastritis. Mention its types and causes.

Q. Define chronic gastritis. (SU-10Ju) **Write down the pathogenesis and clinical features of gastritis.** ***(Very Important for VIVA)***

Ans.

Gastritis: Gastritis is simply defined as **inflammation of the gastric mucosa.**

Types of gastritis:

1. **Acute gastritis:** Acidic damage to the stomach mucosa due to imbalance between mucosal defenses and acidic environment. Acid damage results in **superficial inflammation, mucosal erosion** (loss of superficial epithelium), or **ulcer** (loss of mucosal layer).

   Causes / risk factors: Acute gastritis is frequently associated with-

   - Heavy use of NSAIDs, particularly aspirin
   - Excessive alcohol consumption
   - Ingestion of harsh chemicals, particularly acids or bases, either accidentally or as a suicide attempt
   - Heavy smoking
   - Radiation therapy
   - Chemotherapy
   - Stress-related mucosal diseases
     - *Stress ulcers* – in the setting of shock, sepsis, or severe trauma
     - *Curling ulcer* – in the context of severe burns or trauma
     - *Cushing ulcer* – in association with intracranial disease / brain injury
   - Systemic bacterial or viral infections (e.g. salmonellosis, CMV infection)
   - Mechanical trauma (e.g. nasogastric intubation)
   - Distal gastrectomy
   - Decreased oxygen delivery at high altitude.

Clinical features:

- May be asymptomatic
- Epigastric pain
- Nausea
- Vomiting
- Mucosal erosion
- Ulceration
- Hemorrhage
- Hematemesis
- Malena
- Rarely massive blood loss.

(Ref: Robbins/10th/765; BRS Pathology/5th/230; Pathoma/2014/104)

2. **Chronic gastritis:** Chronic gastritis is characterized by **chronic mucosal inflammation** and **atrophy of the mucosal glands.**

   In contrast to acute gastritis, the symptoms associated with chronic gastritis are typically **less severe** but **more persistent.**

   Causes / risk factors: Chronic gastritis is frequently associated with-

   - *H. pylori* infection
   - Autoimmune gastritis
   - Radiation injury
   - Chronic bile reflux
   - Mechanical injury (e.g. an indwelling nasogastric tube)
   - Systemic diseases, such as Crohn disease, amyloidosis, or graft-versus-host disease.

   Types: Divided into *two types* based on underlying etiology-

   a. ***H. pylori* gastritis:** It is due to ***H. pylori*** induced **acute** and **chronic inflammation.** It is the **most common** form of gastritis (90%). The **antrum** is the **most commonly infected site** for *H. pylori* gastritis.

      Clinical features: Epigastric abdominal pain.

      Sequelae:

      - Peptic ulcer disease (PUD)
      - Gastric adenocarcinoma (intestinal type)
      - MALT lymphoma (MALToma)

      Treatment: Triple therapy (combinations of antibiotics and proton pump inhibitors).

   b. **Autoimmune atrophic gastritis:** It is due to ***autoimmune destruction*** of **gastric parietal cells,** which are located in the stomach **body** and **fundus.** It is associated with the presence of **antibodies** to gastric **parietal cells** and/or **intrinsic factor,** followed by **vitamin B_{12} deficiency** and defective gastric acid secretion **(achlorhydria).**

      Median age at diagnosis is 60 (slightly more women than men are affected).

      Clinical features: Clinical features are mainly related to ***vitamin B_{12} deficiency***, including-

      - Pernicious anemia (a form of megaloblastic anemia)
      - Atrophic glossitis (in which the tongue becomes smooth and beefy red)
      - Epithelial megaloblastosis
      - Malabsorptive diarrhea
      - CNS features of vitamin B_{12} deficiency (e.g. subacute combined degeneration of spinal cord)
      - It is often associated with other autoimmune diseases including Hashimoto thyroiditis, type 1 diabetes mellitus, Addison disease etc.

Sequelae: Intestinal metaplasia (termed *autoimmune metaplastic atrophic gastritis*) leading to increased risk of gastric adenocarcinoma (intestinal type).

(Ref: Robbins/10th/765-769; BRS Pathology/5th/230; Pathoma/2014/104)

Q. Mention the complications of chronic gastritis.

Ans.

Complications of chronic gastritis:

1. Peptic ulcers disease (PUD)
2. Mucosal atrophy and intestinal metaplasia leading to gastric adenocarcinoma
3. Dysplasia (leading to preinvasive in situ carcinoma)
4. MALT lymphoma (MALToma) (*H. pylori* associated)
5. Gastritis cystica (gastritis cystica polyposa & gastritis cystica profunda).

(Ref: Robbins/10th/765-769; BRS Pathology/5th/230; Pathoma/2014/104)

(***N.B:*** The risk of **adenocarcinoma** is greatest in **autoimmune gastritis.**)

(Ref: Robbins/9th/766)

Nice to Know:

Gastropathy: Inflammation of the gastric mucosa occurs in many conditions, and it is called "acute gastritis" when neutrophils are present and "**gastropathy**" when **inflammatory cells** are **rare or absent.**

It includes a diverse set of disorders marked by gastric injury or dysfunction.

Most common agents (irritants) that cause gastropathy include:

- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Alcohol
- Bile.

Gastropathy may be asymptomatic or associated with epigastric pain, nausea, and vomiting. In more severe cases there may be mucosal erosion, ulceration, hemorrhage, hematemesis, melena, or, rarely, massive blood loss.

(Ref: Robbins/10th/765)

(***N.B:*** The term ***hypertrophic gastropathy*** is applied to a specific group of diseases exemplified by **Ménétrier disease** and **Zollinger-Ellison Syndrome**.)

(Ref: Robbins/10th/771)

Q. Mention the characteristics of *Helicobacter pylori*–associated and autoimmune gastritis.

Q. Mention the morphology of chronic gastritis. (SU-10Ju)

Ans.

Characteristics of *Helicobacter pylori*–associated and autoimmune gastritis: *(Important for VIVA)*

Traits	*H. pylori* associated gastritis	Autoimmune atrophic gastritis
1. Location	Antrum	Body
2. Inflammatory infiltrate	Neutrophils, subepithelial plasma cells	Lymphocytes, macrophages
3. Acid production	Increased to slightly decreased	Decreased
4. Gastrin secretion	Normal to increased	Increased to markedly increased
5. Other lesions	Hyperplastic/inflammatory polyps	Neuroendocrine hyperplasia
6. Serology	Antibodies to *H. pylori*	Antibodies to parietal cells (H^+, K^+-ATPase, intrinsic factor)
7. Sequelae	▪ Peptic ulcer ▪ Adenocarcinoma ▪ MALToma	▪ Atrophy ▪ Pernicious anemia ▪ Adenocarcinoma

		▪ Carcinoid tumor
8. Associations	▪ Low socioeconomic status ▪ Poverty ▪ Residence in rural areas	▪ Autoimmune disease ▪ Thyroiditis ▪ Diabetes mellitus ▪ Graves disease
9. Main morphologic features	▪ Gastric biopsy specimen generally demonstrates *H. pylori* in infected individuals. ▪ The antrum is the preferred biopsy site for evaluation of *H. pylori* gastritis because it is most commonly infected.	▪ Autoimmune gastritis is characterized by diffuse mucosal damage of the oxyntic (acid-producing) mucosa within the body and fundus. ▪ The antrum and cardia are typically spared.

(Ref: Robbins/10th/768)

Ulcer

Q. Define ulcer. (CU-08Ju,07Ja)
Ans.
Ulcer: An ulcer is a local defect, or excavation, of the surface of an organ or tissue that is produced by the sloughing (shedding) of inflamed necrotic tissue.

(Ref: Robbins/10th/94)

Q. Enumerate different ulcers / ulcerative lesions in GIT (gastrointestinal tract). (DU-23/22Nv,21Oct/M,18Nv,17Ja,06M, RU-17M,13/11/10/09Ju,08/07Ja, SU-09Ju,07Ja)
Q. Enumerate the ulcers of stomach. (SU-07Ju)
Q. Name 5/4 ulcerative diseases of stomach. (SU-14/13/12Ja)
Q. Enumerate ulcers in the esophagus and large intestine. (RU-16Ju)
Q. Short note: Ulcers of small and large gut. (RU-16Ja)
Q. Short note: Ulcers of GI tract. (RU-18M)
Ans.
Ulcers of the GIT:

A) Ulcers of esophagus & stomach:

a. Benign:
- Chronic gastric ulcer (peptic ulcer)
- Acute gastric ulcers
  - **Stress ulcers** (in the setting of shock, sepsis, or severe trauma)
  - **Curling ulcers** (in the context of severe burns or trauma)
  - **Cushing's ulcers** (in association with intracranial disease / brain injury)

b. Malignant: Ulcerative or excavated gastric carcinoma.

B) Ulcers of small intestine:
- Chronic duodenal ulcer
- Typhoid ulcer
- Tuberculous ulcer
- Crohn's disease
- Malignant ulcers
- Peptic ulcer in Meckel's diverticulum

C) Ulcers of large intestine:
- Amoebic dysentery ulcer
- Bacillary dysentery ulcer
- Malignant ulcer

- Ulcerative colitis
- Tuberculous ulcer
- Typhoid ulcer.

Q. Name the common ulcers of GIT. (RMU-22M,19M,10Ju,07Ja)
Ans.
Common ulcers of GIT:

- Peptic ulcer
- Amoebic dysentery ulcer
- Bacillary dysentery ulcer
- Malignant ulcer
- Tubercular ulcer
- Typhoid ulcer.

Q. Define peptic ulcer / peptic ulcer disease (PUD). (DU-19/17Nv,14/13/11/07Ja, RU-21/20/19/18Nv,16/15/14/13Ja,09Ju, CU-13Ju,10Ja,08Ju)
Q. Enumerate the types of peptic ulcer disease (PUD). (SU-10Ja)
Q. Mention the sites of peptic ulcer formation. (DU-17Nv,14Ja, CMU-22Nv,12/10Ja, RU-19Nv,13Ja, SU-11Ju,10/08Ja)
Q. What are the common sites of peptic ulcer? (DU-15Ja, RMU-22/21/18Nv,15Ja, CMU-21M,16Ju,14Ja,13Ju)
Ans.
Peptic ulcer disease (PUD): Peptic ulcer disease (PUD) refers to **chronic mucosal ulceration** affecting the **duodenum** or **stomach** and is almost always associated with ***H. pylori*** infection, **NSAIDs**, or **cigarette smoking**.
(Ref: Robbins/10th/770)

Or,

Peptic ulcers are the **areas of degeneration and necrosis** of **gastrointestinal mucosa** exposed to **acid-peptic secretions.**
(Ref: Harsh Mohan/7th/533)

Though they can occur at any level of the alimentary tract that is exposed to HCl and pepsin, they occur ***most commonly (98-99%)*** in either the ***duodenum*** or the ***stomach*** in the ratio of 4:1.

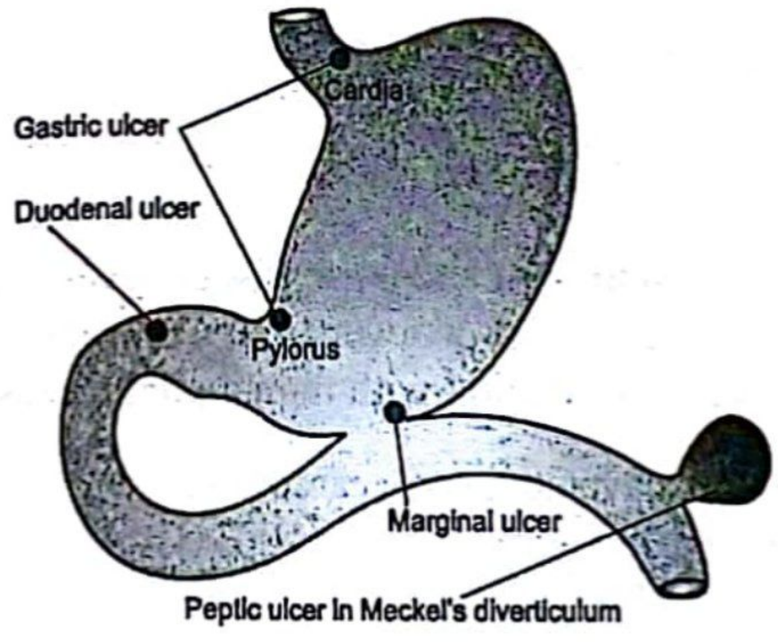


Fig: Distribution of peptic ulcers.

Common sites of peptic ulcer: ***(Important for VIVA)***

1. First part of duodenum
2. Stomach (usually antrum)
3. Gastro-oesophageal junction
4. Within the margins of a gastro-jejunostomy (marginal ulcer)
5. Throughout the GIT in Zollinger-Ellison syndrome
6. Within or adjacent to an ileal Meckel's diverticulum that contains ectopic gastric mucosa.

(Ref: Robbins/10th/770; Harsh Mohan/7th/535)

Q. Write the predisposing factors for peptic ulcer. (DU-21Oct/M,18Nv/Ja)
Q. Enumerate the causes of ulcers in GI tract. (DU-22/17Nv)
Q. What are the causes / risk factors of peptic ulcer disease? (SMU-23/22M, CU-13Ju)
Ans.

Causes / risk factors for peptic ulcer disease: ***(Important for VIVA)***

- *H. pylori* infection (around 90% of duodenal ulcer patients and 70% of gastric ulcer patients are infected with *H. pylori*)
- Cigarette smoking
- NSAIDs (potentiated by corticosteroids)
- Chronic obstructive pulmonary disease
- Illicit drugs, e.g. cocaine, that reduce mucosal blood flow
- Alcoholic cirrhosis (primarily duodenal PUD)
- Psychological stress (can increase gastric acid secretion)
- Endocrine cell hyperplasia (can stimulate parietal cell growth and gastric acid secretion)
- Zollinger-Ellison Syndrome (PUD of stomach, duodenum, and jejunum)
- Viral infection (CMV, herpes simplex virus).

(Ref: Robbins/10th/770; Davidson's/23rd/798)

Q. Mention the defense mechanisms of gastro-duodenal mucosa. (RU-09Ju)
Q. Write down the defense mechanisms of gastric mucosa. (RMU-21M)
Q. How mucosal barrier protects the gastric mucosa from autodigestion?
Ans.

Defense mechanisms of gastro-duodenal mucosa / mucosal barrier: ***(Very Important for VIVA)***

1. Surface mucous secretion
2. Bicarbonate (HCO_3^-) secretion into mucus
3. Increased mucosal blood flow that washes out H^+
4. Intercellular tight junction provides an epithelial barrier to back diffusion to H^+
5. Apical surface membrane transport
6. Quick regenerative capacity of lining epithelium
7. Elaboration of prostaglandin that increases mucus secretion, blood flow and epithelial regeneration.

(Ref: Robbins/10th/765; Lecture SSMC)

Q. Describe briefly the pathogenesis of peptic ulcer disease. (DU-22Nv, CMU-22M,19M,13Ja,08Ju,07Ja, RU-19Nv,18M,16/15Ja,11Ju, SU-14/12Ja,09Ju)
Ans.

Pathogenesis of peptic ulcer disease: PUD results from ***imbalances*** between-

- ***Mucosal defense mechanisms*** (protective factors) &
- ***Damaging forces that cause chronic gastritis***

(***N.B:*** PUD generally develops on a background of chronic gastritis.)

1. **Impairment of defense mechanism:** By the followings- ***(Very Important for VIVA)***
   - ↓ Mucus secretion
   - ↓ Bicarbonate secretion in mucus
   - ↓ Mucosal blood flow
   - ↓ Apical surface membrane transport
   - ↓ Epithelial regenerative capacity
   - ↓ Prostaglandin elaboration
2. **Increased damaging forces:**
   - Gastric hyperacidity
   - Peptic enzymes
   - *Helicobacter pylori* infection

- NSAID
- Aspirin
- Cigarettes
- Alcohol
- Duodenal gastric reflux.

(Ref: Robbins/10th/765,770)

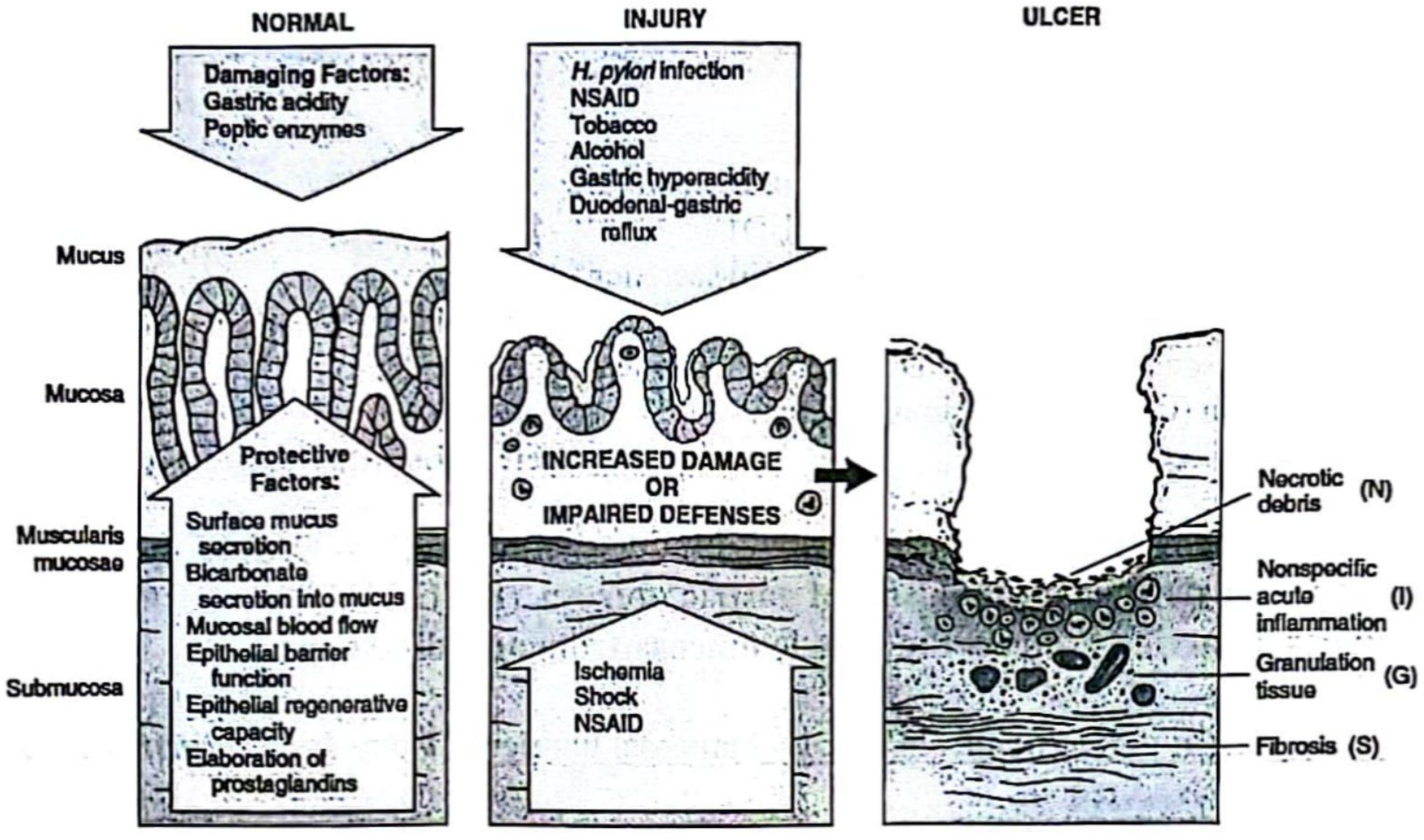


Fig: Pathogenesis of peptic ulcer disease (mechanisms of gastric injury and protection).

Q. What are the diseases associated with *H. pylori* infection? (SU-20Nv,15Ja,08Ju)
Q. Enumerate the *H. pylori* related diseases in stomach? (SU-13Ju,11Ja)
Q. Enumerate the *H. pylori* associated diseases of GIT. (SMU-23/22M)
Ans.

Diseases associated with *H. pylori* infection: *(Important for VIVA)*

1. Peptic ulcer disease (PUD)
2. Chronic gastritis
3. Gastric carcinoma
4. Gastric lymphoma / MALToma.

(Ref: Robbins/10th/767)

Q. What is the role of *H. pylori* in the pathogenesis of peptic ulcer? (CU-12Ja, SU-13Ju,11/Ja,08Ju)
Q. *H. pylori* does not invade the tissue, but it can cause peptic ulcer. Explain. (DU-08Ju)
Ans.

Role of H. pylori in the pathogenesis of peptic ulcer: *(Important for VIVA)*

1. Although *H. pylori* do not invade the tissues, it induces an ***intense inflammatory and immune response*** and liberates ***proinflammatory cytokines*** such as IL-1, IL-6, IL-8 and tumour necrosis factor-α (TNF-α).
2. It secretes ***urease*** enzyme that breaks down urea to form toxin compounds such as ammonium chloride and monochloramine.
3. Bacterial ***proteases*** and ***phospholipases*** breakdown the glycoprotein-lipid complexes in the gastric mucus, thus weakening the first line mucosal defense.
4. It ***enhances gastric acid secretion*** and ***impairs duodenal bicarbonate production***.

5. Thrombotic occlusion of surface capillaries is promoted by bacterial ***platelet activating factor.***
6. Bacterial antigens (including lipopolysaccharide) recruit inflammatory cells to the mucosa.

(***N.B: H. pylori*** infection most often presents as a predominantly **antral gastritis** with normal or increased acid production.)

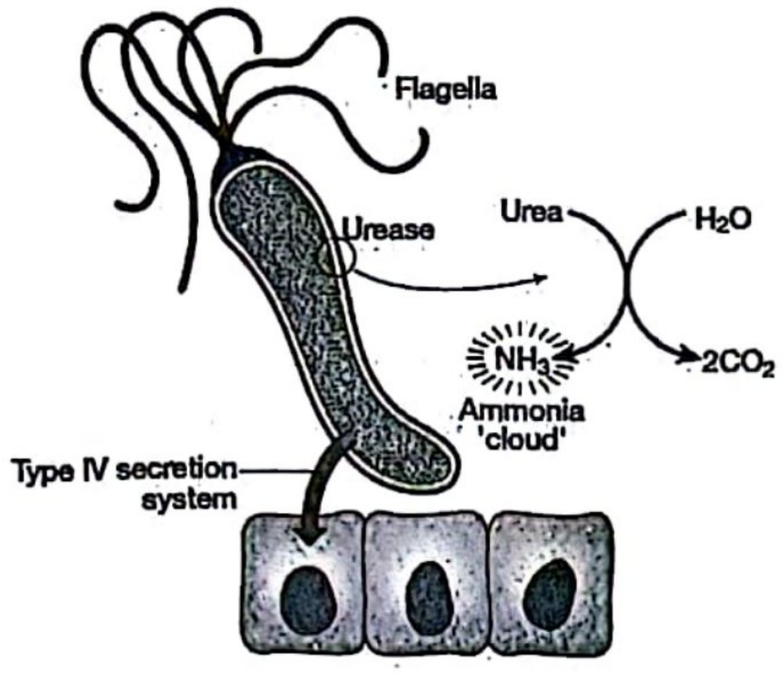


Fig: Damaging effects of *H. Pylori* in stomach.

(Ref: Robbins/10th/767)

Q. What are the tests done for *H. pylori* infection?

Ans.

Tests for *H. pylori*: *(Important for MCQ)*

1. **Non-invasive test:**
   - Serological test for antibodies to *H. pylori*
   - Faecal antigen test
   - ^{13}C-urea breath test
2. **Invasive test (antral biopsy):**
   - Detection of *H. pylori* in gastric biopsy tissue
   - Rapid urease test
   - Bacterial culture
   - PCR-based detection of *H. pylori* DNA.

(Ref: Robbins/10th/768; Davidson's/23rd/800; Lecture SSMC)

Q. Write down the morphology of peptic ulcer. (DU-13/11Ja,09Ju, SMU-23/22M,20Nv, RU-11Ju)
Q. Write the morphology of peptic ulcer disease with diagram. (SU-13/10Ja)
Q. Write the microscopic features of peptic ulcer. (DU-14Ja, CMU-22Nv,14Ja)
Q. Write down the histopathological features of peptic ulcer disease. (SU-15Ja)
Q. Write the histologic findings of peptic ulcer. (CU-18Nv,16Ju)

Ans.

Pathology / morphological feature of peptic ulcer: Gross and microscopic changes in gastric and duodenal ulcers are similar and quite characteristic.

Gross / macroscopic:

Location:

- ***Gastric ulcer*** - Predominantly along the ***lesser curvature*** in the region of ***pyloric antrum***, more commonly on the ***posterior*** than the anterior wall.
- ***Duodenal ulcer*** - Mostly in the ***first part*** of the duodenum, more commonly on the ***anterior*** than the posterior wall.

Shape: Round to oval, sharply punched-out defect.

Margin:

- Usually levels with surrounding mucosa or only slightly elevated.
- Mucosal margin may overhang the base slightly.

Depth:

- Superficial ulcers - confined to mucosa.
- Deep ulcers - penetrating into the muscular layer (muscularis propria).

Base:

- Smooth and clean due to peptic digestion of the exudates.
- Blood vessels may be evident.

Microscopic: 4 histological zones (from within outside)-

i. Superficial thin layer of necrotic fibrinoid debris.
ii. Zone of non specific inflammatory infiltrate, with neutrophils predominating.
iii. Zone of active granulation tissue infiltrated with mononuclear leucocytes.
iv. A base of scar tissue.

(Ref: Robbins/10th/770; Harsh Mohan/7th/535)

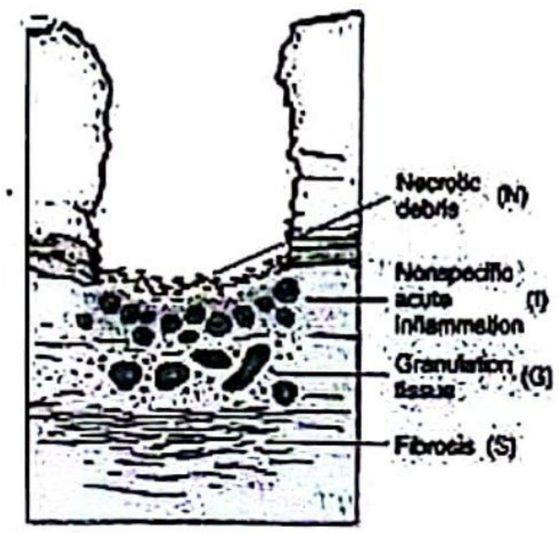
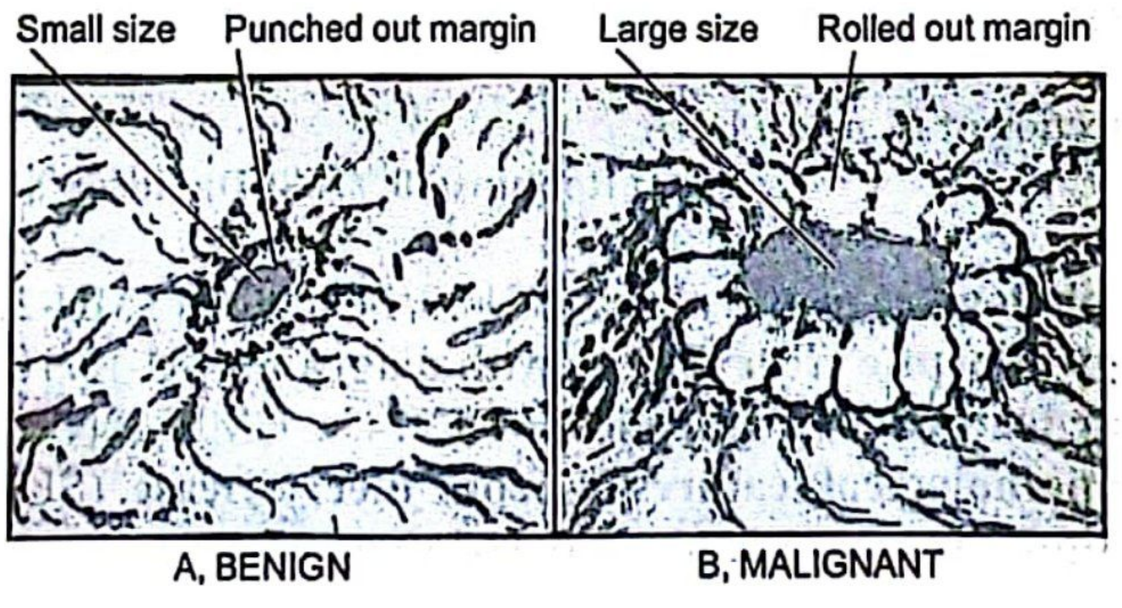


Fig: Microscopic zones of peptic ulcer.

***(N.B:** Malignant gastric ulcers are larger, bowl-shaped with elevated and indurated mucosa at the margin.)*
(Ref: Harsh Mohan/7th/535)



Q. How you can differentiate a benign ulcer from a malignant one? (DU-18Nv/Ja,17Nv, RU-21/19Nv,18/17M,14Ja,08Ju, CU-14Ja)
Q. Mention the differentiating points in between a benign and a malignant ulcer. (DU-23/19Nv, RMU-22Nv,05M)
Q. How a benign ulcer differs from a malignant ulcer morphologically? (DU-21Oct/M)
Ans.
Differences between a benign (peptic ulcer) and a malignant ulcer: (V.V.I. for VIVA)

Traits	Benign (peptic) ulcer	Malignant ulcer
1. Age	Usually younger age	Usually older age

2. Sex	Marked male predominance	Slight male predominance
3. Duration of symptoms	Longer (weeks to years)	Shorter (weeks to months)
4. Location of lesion	Usually lesser curvature of pylorus and antrum	Usually greater curvature of pylorus and antrum
5. Gross features		
▪ **Size**	Small	Large
▪ **Shape**	Regular	Irregular
▪ **Margin**	Sharply demarcated (punched out)	Thickened, irregular & rolled out
▪ **Ulcer bed**	More or less clear; necrosis & haemorrhage uncommon	Necrosis & haemorrhage are commonly present
6. Gastric acidity	Normal or increased	Normal, but can be totally absent (achlorhydria)
7. Response to medical therapy	Satisfactory	May respond, but refractory
8. X-ray finding	Small punched out defect without involvement of surrounding mucosa	An irregular filling defect and possible involvement of surrounding mucosa

(Ref: Harsh Mohan/7th/543; Lecture DMC & RMC)

Q. Mention the clinical features of peptic ulcer disease. (V.V.I. for VIVA)

Ans.

Clinical features of peptic ulcer disease: Peptic ulcers are ***remitting*** and ***relapsing*** lesions.

1. **Periodic epigastric pain** - burning or aching pain {in ***gastric ulcer***, pain occurs immediately or within 1 to 3 hours after food during the ***day*** and ***never occurs at night***. In ***duodenal ulcer***, pain is severe, occurs at ***late night*** (usually between 11 p.m. and 2 a.m.) (**'hunger pain'**), and is usually ***relieved by alkali or food***}.
2. **Nausea, vomiting, bloating, belching, heart-burn** *(retrosternal pain)* and **'water brash'** (*burning fluid into the mouth*)
3. **Anorexia** and **early satiety** after meals
4. **Weight loss** in gastric ulcer patients & **weight gain** in duodenal ulcer patients
5. **Haematemesis** and **melaena**
6. **Iron deficiency anemia**
7. **Acute perforation.**

(***N.B:*** With penetrating ulcers the pain is occasionally referred to the back, left upper quadrant, or chest, where it may be misinterpreted as cardiac in origin.).

(Ref: Robbins/10th/771; Harsh Mohan/7th/536; Davidson's/23rd/799)

Q. Write down the complications of peptic ulcer / peptic ulcer disease (PUD). (DU-22/19Nv,15/14/13/11Ja, RU-21/20/18Nv,17Ju/M,16/15/14Ja,11/09Ju,07Ja, CU-10Ja)

Q. Write down the important complications of peptic ulcer. (DU-23Nv)

Q. Short note: Complications of peptic ulcer. (RU-18M,11Ju)

Ans.

Complications of peptic ulcer: (V.V.I. for VIVA)

1. **Bleeding:**
   - Occurs in 15-20% of patients
   - Most frequent complication
   - May be life-threatening
   - Accounts for 25% of ulcer-related deaths
   - May be the 1st indication of an ulcer
2. **Perforation:**

- Occurs in up to 5% of patients
- Accounts for two-thirds of ulcer-related deaths
- Is rarely 1st indication of an ulcer

3. **Obstruction:**
   - Mostly in chronic ulcers
   - Secondary to edema and scarring
   - Occurs in about 2% of patients
   - Most often associated with pyloric channel ulcers
   - May occur with duodenal ulcers
   - Causes incapacitating, crampy abdominal pain
   - Can rarely cause total obstruction and intractable vomiting
4. **Malignant transformation:** A ***chronic duodenal ulcer never turns malignant,*** while ***chronic gastric ulcer may develop carcinoma in less than 1% of cases.***

(Ref: Robbins/10th/771; Harsh Mohan/7th/535)

Q. Short note: Peptic ulcer. (CU-14Ju, RU-08Ja)

Ans.

Peptic ulcer: *Please write from above.*

Q. Mention the differentiating points in between duodenal and gastric ulcer. (For VIVA)

Ans.

Differentiating points in between duodenal and gastric ulcer:

Traits	Duodenal ulcer	Gastric ulcer
1. Incidence	4 times more common than gastric ulcers	Less common than duodenal ulcers
2. Usual age	25-50 years	Usually beyond 6th decade
3. Etiology	Most commonly as a result of *H. pylori* infection	Disruption of mucus barrier most important factor in association with gastritis, bile reflux, drugs, alcohol, tobacco etc.
4. Clinical features	a. Pain-food-relief pattern b. Night pain common c. No vomiting d. Melaena more common than haematemesis e. No loss of weight f. No particular choice of diet g. Deep tenderness in the right hypochondrium h. Marked seasonal variation i. Occurs more commonly in people at greater stress	a. Food-pain pattern b. No night pain c. Vomiting common d. Haematemesis more common e. Significant loss of weight f. Patients choose bland diet devoid of fried foods, curries etc. g. Deep tenderness in the midline in epigastrium h. No seasonal variation i. More often in labouring groups
5. Pathologic changes	Most common in the first part of duodenum	Most common along the lesser curvature and pyloric antrum
6. Malignant transformation	Never occurs	in less than 1% cases

(Ref: Harsh Mohan/7th/534; Lecture DMC & RMC)

Q. A man of 30 years complains of epigastric pain following meals and at late hours of night along with nausea and vomiting. What is the likely diagnosis? What complications can occur with this disease? (DU-19M)

Ans.

Likely diagnosis: Peptic ulcer disease (PUD).

Complications: *Please write from above.*

Gastrointestinal Stromal Tumor (GIST)

Q. Short note: Gastrointestinal stromal tumor (GIST). (DU-21Ja,20Nv/M)

Ans.

Gastrointestinal stromal tumor (GIST): Gastrointestinal stromal tumors (GISTs) are **mesenchymal tumors** derived from the ***interstitial cells of Cajal***, or ***pacemaker cells*** of the ***gastrointestinal muscularis propria***.

It is the ***most common mesenchymal tumor of the abdomen***, with annual incidences between 11 and 20 per million people.

Age of incidence: GISTs are diagnosed at a **peak age** of **60 years**, with fewer than 10% occurring before 40 years of age.

Site of occurrence: More than half of these tumors occur in the ***stomach***.They can also occur in the ***small intestine***, ***large intestine***, and ***extragastrointestinal sites***.

Behaviour: Their behaviour is ***generally benign*** but may be ***recurrent***, ***aggressive*** or even ***metastasis*** may occur.

Genetic mutation:

- c-kit oncogene (CD117) - detected by immunohistochemistry from Cajal cells
- Platelet-derived growth factor receptor-α (PDGFRA)

Morphology:

Gross:

- Primary gastric GISTs can reach 30 cm in diameter.
- They usually form a solitary, well-circumscribed, fleshy mass.
- The overlying mucosa is frequently ulcerated, and the cut tumor surface has a whorled appearance.

Microscopic:

- GISTs composed of thin elongated cells are classified as **spindle cell type**, while GISTs dominated by plumper, epithelial-appearing cells are termed **epithelioid type**; mixtures of the two patterns are common.

Symptoms:

- Mass effects
- Mucosal ulceration causing blood loss leading to anemia or related symptoms.

Diagnosis: GISTs may be discovered incidentally during radiologic imaging, endoscopy, or abdominal surgery performed for other reasons.

Treatment:

- Complete surgical resection (primary treatment for localized GIST)
- Targeted therapy / tyrosine kinase inhibitor (imatinib) - which inhibits the tyrosine kinase activity of c-kit and PDGFRA.

(Ref: Robbins/10th/779; BRS Pathology/5th/232; Harsh Mohan/7th/538)

Carcinoma of Stomach

Adenocarcinoma is the **most common malignancy of the stomach,** comprising more than **90%** of all gastric cancers.

(Ref: Robbins/10th/774)

Q. Mention the sites of gastric carcinoma.

Ans.

Sites of gastric carcinoma: Gastric carcinoma is **most commonly** located in the region of **gastric canal** (prepyloric region) formed by **lesser curvature, pylorus** and **antrum**. Other less common locations are the body, cardia and fundus.

1. Pylorus and antrum (50 - 60%)
2. Cardia (25%)
3. Body and fundus (15 - 25%).

(***N.B*:** Histologically, **gastric carcinoma** is almost always **adenocarcinoma**.)

(Ref: Robbins/10th/774; Harsh Mohan/7th/538)

Nice to Know:

Gastric carcinomas are broadly classified into two main groups:

1. **Early gastric carcinoma** (tumour is confined to the mucosa and submucosa)
2. **Advanced gastric carcinoma** (extends into the muscularis propria and beyond).

(Ref: Harsh Mohan/7th/539)

Gastric adenocarcinoma is separated morphologically into two types:

1. **Intestinal type,** which tends to form bulky masses
2. **Diffuse type,** which infiltrates and thickens the gastric wall.

(Ref: Robbins/10th/774)

Q. Mention the risk factors of gastric carcinoma. (BUP-22/19M,16Ja, CU-17Nv)

Ans.

Risk factors of gastric carcinoma: ***(Important for VIVA)***

1. **Environmental factors:**
   - **Geographic area:** Incidence varies greatly from one geographic area to another, with much higher incidence in **Japan, Finland,** and **Iceland**
   - Ingestion of **smoked foods**
   - High intake of carcinogens as **nitrates** in foods and drinking water, **nitrites** as preservatives for certain meats etc.
   - Diet with **smoked fish & meat,** and **pickled raw vegetables**
   - Excessive **salt intake** and a diet **low** in **fresh fruits** and **vegetables**
   - Low socio-economic status
   - Cigarette **smoking** & consumption of **alcohol**
2. **Host factors:**
   - **Age:** Most common **after 50 years of age**
   - **Sex:** Common in **men** than women
   - ***H. pylori*** infection
   - **Achlorhydria**
   - **Chronic gastritis** with or without **pernicious anemia**
   - **Gastric adenoma**
   - **Partial gastrectomy** (stump carcinoma)
   - **Chronic gastric ulcer** (ulcer-cancer)

3. **Genetic factors:**
   - Slightly increased risk with **blood group-A**
   - **Family history** of gastric cancer
   - **Hereditary nonpolyposis colon cancer syndrome**
   - Familial gastric carcinoma syndrome **(E-cadherin mutation).**

(Ref: Robbins/10th/774; BRS Pathology/5th/231; Pathoma Lecture Notes; Harsh Mohan/7th/538)

*{**N.B:** Individuals with **blood group A** have higher tendency to develop **gAstric cancer** (On the other hand **peptic ulcer** is more common in individuals with **blood group O**)}.*

(Ref: Harsh Mohan/7th/538)

Q. Write down the role of *H. pylori* in gastric carcinoma. (CU-12Ja)

Ans.

Role of *H. pylori* in gastric carcinoma: *(Important for VIVA)*

H. pylori infection
↓
Disruption of normal gastric and duodenal protective mechanisms
↓
Chronic gastritis
↓
Over time chronic antral *H. pylori* gastritis may progress to pangastritis, resulting in multifocal atrophic gastritis
↓
Reduced acid secretion
↓
Intestinal metaplasia/dysplasia
↓
Increased risk of gastric adenocarcinoma.

(Ref: Robbins/10th/775)

Q. Mention the clinical features of gastric carcinoma.

Ans.

Clinical features of gastric carcinoma:

1. **Early symptoms:**
   - Dyspepsia
   - Dysphagia
   - Nausea
2. **Advanced stages:**
   - Abdominal pain
   - Weight loss (cachexia)
   - Anorexia
   - Early satiety
   - Anemia
   - Altered bowel habits
   - Hemorrhage (in the form of haematemesis and/or melaena).

(Ref: Robbins/10th/774; Pathoma Lecture Notes; Harsh Mohan/7th/542)

Q. Discuss the morphology of gastric carcinoma. (RU-07Ju)
Q. Give the histological findings of gastric carcinoma. (SU-08Ja)
Q. Mention the macroscopic and microscopic types of gastric carcinoma. (CU-17M)
Q. Mention the gross and histologic features of gastric adenocarcinoma. (CMU-23M)
Q. Give the morphologic characteristics of malignant ulcer of stomach. (RU-10Ju)

Ans.

Morphology of gastric carcinoma:

Gross / macroscopic: The three macroscopic growth patterns of gastric carcinoma, which may be evident at both the ***early*** and ***advanced stages***, are-

1. **Exophytic:** Protrusion of tumor mass into the lumen.
2. **Flat or depressed:** No obvious tumor mass is visible within the mucosa.
3. **Excavated:** Shallow or deep ulcer present in the wall of the stomach.

When there are large areas of infiltration, diffuse rugal flattening and a rigid, thickened wall may impart a **"leather bottle"** appearance termed **linitis plastica.**

Microscopic:

a. **Intestinal type:** More common.
   - **Expanding** growth pattern
   - Bulky tumors, composed of **columnar, gland-forming cells**
   - Abundant mucin may be present in gland lumens

b. **Diffuse type:**
   - **Infiltrative** growth pattern
   - Composed of **signet-ring cells** (that diffusely infiltrate the gastric mucosa)
   - **Excessive mucin** production.

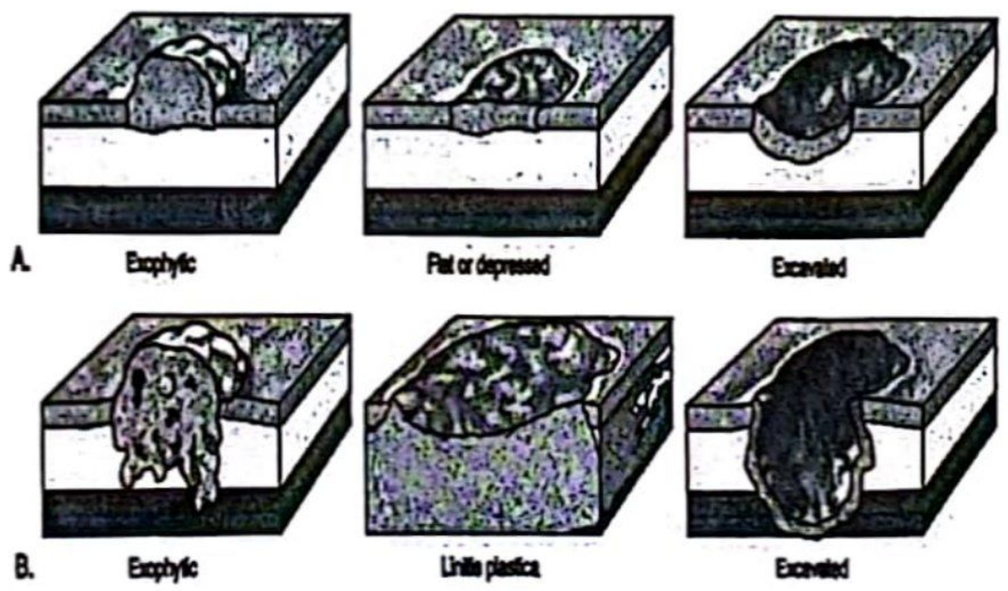


Fig: Morphology of gastric carcinoma.
(Note: A. Early gastric carcinoma; B. Advanced gastric carcinoma)
(Ref: Robbins/10th/775)

Q. What is linitis plastica? (CU-06M)

Ans.

Linitis plastica: When there are large areas of infiltration, ***diffuse rugal flattening*** and a rigid, thickened wall may impart a **"leather bottle"** appearance termed **linitis plastica.**

Or,

Linitis plastica is an extreme form of flat or depressed advanced gastric carcinoma.

Breast and lung cancers that metastasize to the stomach may also create a linitis plastica-like appearance.
(Ref: Robbins/10th/775)

Q. How & where gastric carcinoma spread? (V.V.I. for VIVA)

Ans.

Spread of gastric carcinoma:

1. **Local invasion:** Direct spread by local extension into the neighbouring structures and organs like esophagus, duodenum, lesser and greater omentum, pancreas, liver, spleen, and transverse colon etc.
2. **Metastatic spread:**

- Left supraclavicular lymph node **(Virchow's node)** - ***Troisier's sign*** (sometimes the presenting feature of gastric carcinoma)
- Periumbilical lymph nodes **(Sister Mary Joseph nodule)**
- Transcoelomic dissemination into one or both ovaries **(Krukenberg tumor)**
- Left axillary lymph node
- Pouch of Douglas
- Widespread **peritoneal seeding** and **haematogenous spread** to the liver, lungs, brain, bones, kidneys and adrenals.

(Ref: Robbins/10th/774; Harsh Mohan/7th/541)

Nice to Know: (V.V.I. for VIVA)

- **Krukenberg tumor:** A metastatic ***gastrointestinal neoplasia*** to the ***ovaries*** is termed as **Krukenberg tumor.** *Gastric adenocarcinoma* is the most common source.
- **Sister Mary Joseph nodule:** Gastric tumours can metastasize to the ***periumbilical region*** to form a ***subcutaneous nodule***, termed a **Sister Mary Joseph nodule.**
- **Virchow's node:** Involvement of ***left supraclavicular lymph node*** mainly by **metastatic carcinoma of stomach** (and other **GI malignancies**) is referred to as a **Virchow node** (the so called **"Troiser's sign"**).

(Ref: Robbins/10th/774; BRS Pathology/5th/231; Harsh Mohan/7th/541)

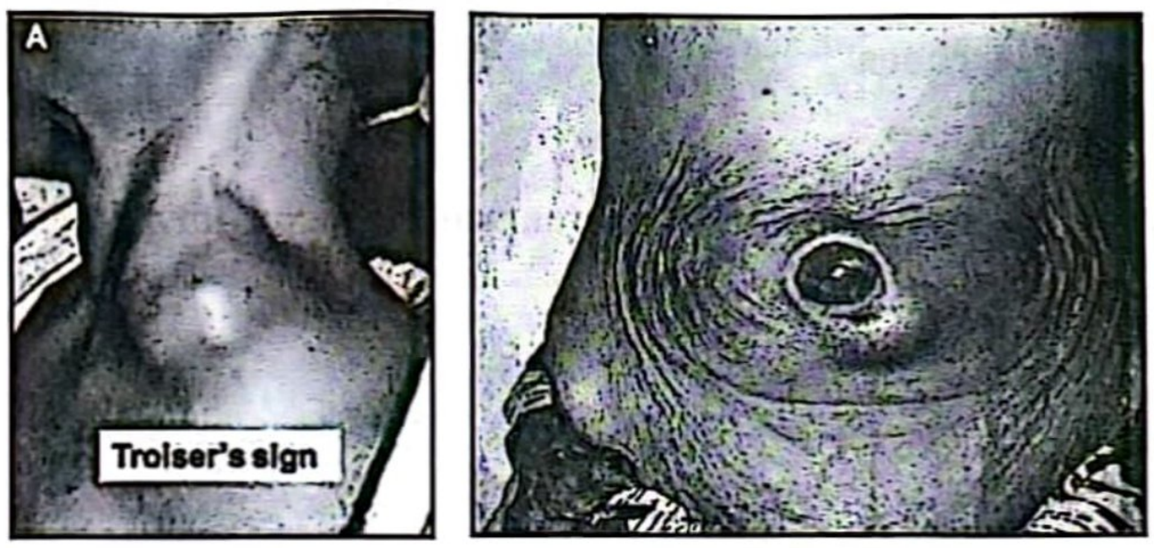


Fig: Left (Virchow node); Right (Sister Mary Joseph nodule).

Q. Short note: Krukenberg tumor. (RU-17M,15Ja,12Ju,10Ja) ***(Very Important for VIVA)***

Ans.

Krukenberg tumor: Metastatic ***gastrointestinal neoplasia*** to the **ovaries** is called **Krukenberg tumor.** It is ***mostly bilateral*** and ***gastric adenocarcinoma*** is the ***most common source***.

Or,

Bilateral involvement of the **ovaries** by **metastatic carcinoma of the stomach** is referred to as **Krukenberg tumors.**

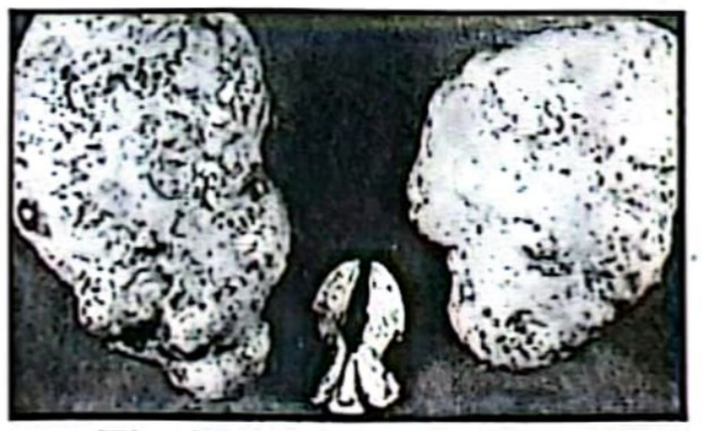


Fig: Krukenberg tumor.

Characteristics: Krukenberg tumor is characterized by-

- **Bilateral** metastasis to the **ovaries**
- Most often **gastric origin** (although it can arise from other tissues such as the **breast**)

- Composed of **mucing-producing, "signet-ring" cells.**

(Ref: Robbins/10th/774,1028; BRS Pathology/5th/231; Harsh Mohan/7th/541)

Small & Large Intestine

Q. Mention the diseases of intestine.
Q. Classify tumors of intestine. (DU-04M,03S)
Ans.
Diseases of intestine:

1. **Congenital anomalies:**
   - Atresia & stenosis
   - Meckel diverticulum
   - Congenital aganglionic megacolon- *Hirschsprung disease*
2. **Intestinal obstruction:**
   - Hernias
   - Adhesions
   - Volvulus
   - Intussusception
3. **Ischemic bowel disease**
4. **Angiodysplasia**
5. **Malabsorption and diarrhoea**
   - Cystic fibrosis
   - Celiac disease
   - Environmental enteric dysfunction / environmental enteropathy / tropical enteropathy / tropical sprue
   - Autoimmune enteropathy
   - Lactase (disaccharidase) deficiency
   - Microvillus inclusion disease / Davidson disease
   - Abetalipoproteinemia
6. **Infectious enterocolitis:**
   - Cholera
   - Campylobacter enterocolitis
   - Shigellosis
   - Salmonellosis
   - Typhoid fever
   - Yersinia
   - E. coli
   - Pseudomembranous colitis
   - Whipple disease
   - Viral gastroenteritis
   - Parasitic enterocolitis
7. **Inflammatory bowel disease (IBD):**
   - Crohn disease
   - Ulcerative colitis
   - Indeterminate colitis
8. **Other causes of chronic colitis:**
   - Diversion colitis
   - Microscopic colitis

9. **Graft-versus-host disease**
10. **Sigmoid diverticular disease**
11. **Hemorrhoids:** Internal and external hemorrhoids.
12. **Acute appendicitis**
13. **<u>Tumors of the small intestine and colon</u>:**
    a. **Polyps:**
       - Hyperplastic polyps
       - Inflammatory polyps
       - Hamartomatous polyps
         - *Juvenile polyps*
         - *Peutz-Jeghers syndrome*
       - Neoplastic polyps

    b. **Familial syndromes:**
       - Familial adenomatous polyposis
       - Hereditary non-polyposis colorectal cancer (HNPCC)

    c. **Neoplastic lesions: *(Very Important for VIVA)***
       - **Small intestine:**
         - **Benign:** Gastrointestinal stromal tumours (GIST), leiomyomas, adenomas and vascular tumours (haemangioma, lymphangioma).
         - **Malignant:** Adenocarcinoma, carcinoid tumours, lymphoma, sarcoma.
       - **Large intestine:**
         - Adenocarcinoma (*most common malignancy of the GI tract*)
         - Other malignant tumours (leiomyosarcoma, malignant lymphoma, carcinoid tumours).

13. **<u>Tumors of the anal canal</u>:**
    - **Benign** (viral warts or condyloma acuminata)
    - **Malignant** (squamous cell carcinoma, adenocarcinoma, malignant melanoma)

14. **<u>Tumors of the appendix</u>:**
    - Carcinoid tumour (most common)
    - Psedo-myxoma peritoneii
    - Adenocarcinoma.

(Ref: Robbins/10th/753,780-819; Harsh Mohan/7th/544-569)

<u>Nice to Know</u>:

<u>Causes of intestinal obstruction</u>: *(Important for VIVA)*

1. **Hernias:** Any weakness or defect in the abdominal wall may permit protrusion of a serosa-lined pouch of peritoneum called a *hernia sac*.
2. **Adhesions:** Surgical procedures, infection, or other causes of peritoneal inflammation, such as endometriosis, may result in development of *adhesions* between bowel segments, the abdominal wall, and operative sites.
3. **Volvulus:** Volvulus occurs when a loop of bowel twists about its mesenteric point of attachment and results in both luminal and vascular compromise. Thus, volvulus presents with features of both obstruction and infarction. It occurs most often in large redundant loops of sigmoid colon, followed in frequency by the cecum, small bowel, stomach, or, rarely, transverse colon.

4. **Intussusception:** It occurs when a segment of the intestine, constricted by a wave of peristalsis, telescopes into the immediately distal segment. Once trapped, the invaginated segment is propelled by peristalsis and pulls the mesentery along. Untreated intussusception may progress to intestinal obstruction, compression of mesenteric vessels, and infarction. Intussusception is the most common cause of intestinal obstruction in children younger than 2 years of age.

(Ref: Robbins/10th/780,781)

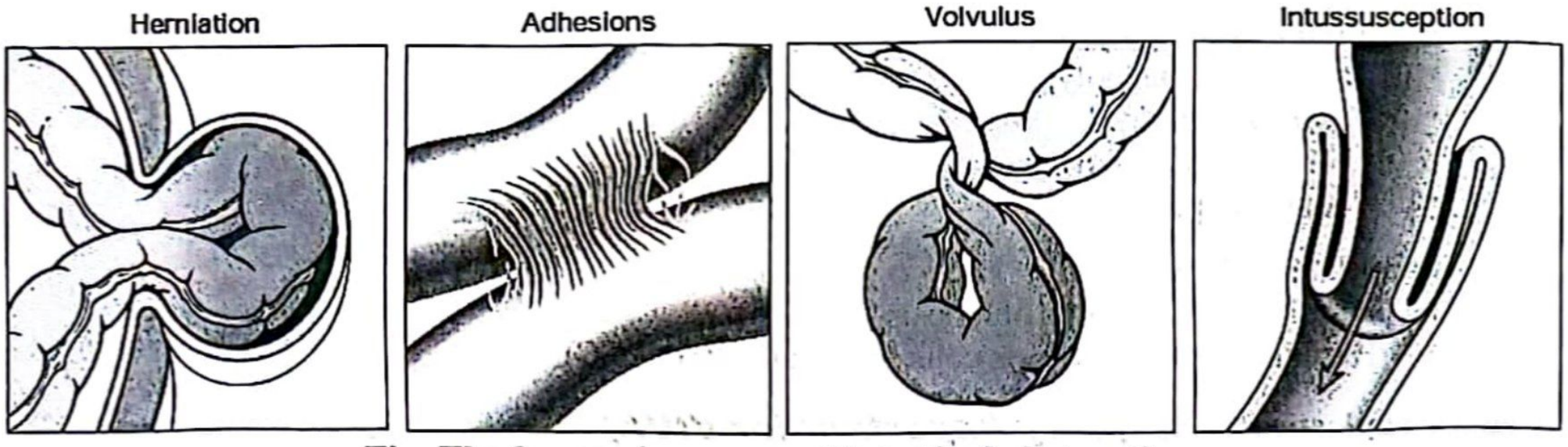


Fig: The four major causes of intestinal obstruction.

Q. List four congenital anomalies of GIT. (DU-17M)

Ans.

Congenital anomalies of GIT: *Please write from above (congenital anomalies of esophagus, stomach, small & large intestine).*

Meckel Diverticulum

Meckel diverticulum: It is the **blind outpouching** of all three layers of the bowel wall **(true diverticulum)** arises due to **incomplete obliteration of *vitellointestinal duct*.**

The **most common congenital anomaly of the GI tract** is Meckel diverticulum, which occurs in the **ileum.**

Characteristics: The **"rule of 2s"** is often used to help remember characteristics of Meckel diverticula, which:

- Occur in approximately 2% of the population
- Are generally present within 2 feet (60 cm) of the ileocecal valve
- Are approximately 2 inches (5 cm) long
- Are twice as common in males
- Are most often symptomatic by age 2 (only approximately 4% are ever symptomatic).

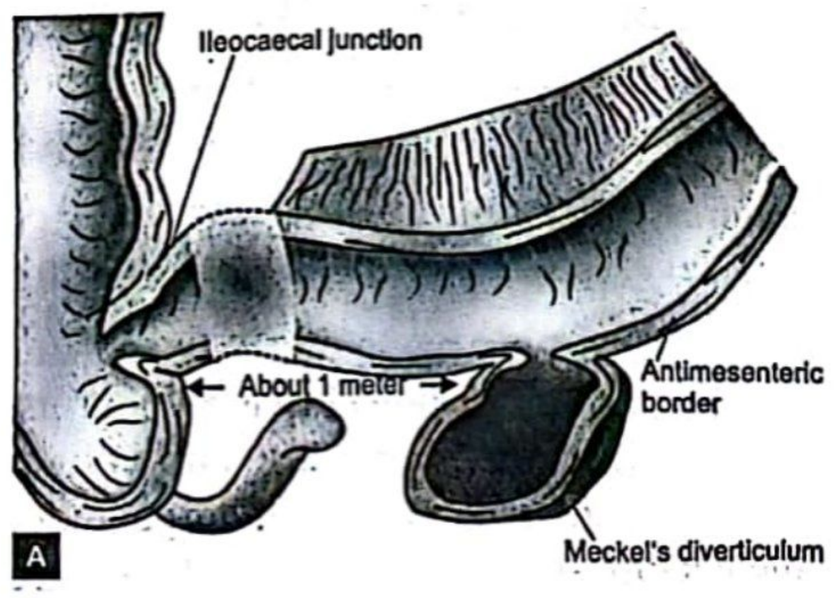


Fig: Meckel's diverticulum (common location and gross appearance).

Lining: It is almost always lined by **small intestinal type of epithelium;** rarely it may contain **islands of gastric mucosa** and **ectopic pancreatic tissue.**

Complications: The common complications of Meckel's diverticulum are ***perforation***, ***haemorrhage*** and ***diverticulitis***.

(Ref: Robbins/10th/755; Pathoma/2014/106; Harsh Mohan/7th/544)

Disorder of Intestinal Motility (Megacolon)

Q. What is megacolon? (CMU-22Nv)

Q. Short note: Megacolon.

Ans.

Megacolon: The term 'megacolon' is used for any form of **marked dilatation** of the **entire colon** or its **segment.**

Types & causes:

1. **Congenital:**
   a) **Hirschsprung's disease (common):** Characterised by **congenital absence of ganglion cells** in the bowel wall (enteric neurons) is called Hirschsprung's disease. As a result, the aganglionic segment remains contracted.
   b) Myopathies, neuropathies (rare).
2. **Acquired:**
   a) **Obstructive:** e.g. due to tumour, post-inflammatory strictures.
   b) **Endocrine:** e.g. in myxoedema, cretinism.
   c) **CNS disorders:** e.g. spina bifida, paraplegia, Parkinsonism etc.
   d) **Psychogenic:** e.g. emotional disturbances, psychiatric disorders etc.
   e) **Connective tissue disease:** e.g. Scleroderma.
   f) **Chagas' disease:** It is (by *Trypanosoma cruzi)* the only example resulting in **acquired loss of ganglion cells.** In all other acquired causes listed above, the bowel innervation is normal.

(Ref: Harsh Mohan/7th/563, 564)

Hirschsprung Disease / Congenital Aganglionic Megacolon

Q. Short note: Hirschsprung disease. (DU-12Ju, CU-15Ja) ***(For VIVA)***

Ans.

Hirschsprung disease / congenital aganglionic megacolon: It is a ***congenital disease*** caused by **absence of ganglion cells** in the nerve plexus (Meissner's & Auerbach's plexus) usually of the **distal hind gut** with hypertrophy of nerve fiber.

Hirschsprung disease causes **functional obstruction** of the **colon.** It occurs in pproximately 1 in 5000 live births.

Pathogenesis: Hirschsprung disease results when the **migration of neural crest cells from cecum to rectum** is **arrested prematurely** or when the **ganglion cells** undergo **premature death.** This produces a distal intestinal segment that lacks both the ***Meissner submucosal plexus*** and the ***Auerbach myenteric plexus***, termed **aganglionosis**. Coordinated peristaltic contractions are absent, and functional obstruction occurs, resulting in dilation proximal to the affected segment.

Sites:

- In about 2/3rd cases, rectum and sigmoid colon are involved
- Ano-rectal junction
- Recto-sigmoid junction
- Whole colon

- Very rarely, portion of terminal ileum.

Clinical features: Clinical features vary from acute intestinal obstruction in neonate to chronic constipation in later life.

1. **In neonate:**
   - Failure to pass meconium
   - Abdominal distension
   - Bilious vomiting
2. **In chronic presentation** (in 1st few weeks of life)**:**
   - Chronic intermittent constipation
   - Gradual abdominal distension
   - Failure to thrive
3. **In adult:**
   - Severe constipation.

Investigations:
- Plain x-ray abdomen
- Barium enema x-ray
- Rectal suction biopsy (reveals lack of ganglion cells)
- Anorectal manometry.

*(**N.B:** Diagnosis of Hirschsprung disease requires **histologic confirmation** that **ganglion cells are absent** within the affected segment.)*

Treatment: Surgical resection of the aganglionic segment and anastomosis of the normal proximal colon to the rectum.

Complication:
- Enterocolitis
- Intestinal obstruction
- Fluid and electrolyte disturbances
- Growth retardation
- Perforation
- Peritonitis
- Septicemia.

(Ref: Robbins/10th/756; Pathoma/2014/109; Lecture SSMC)

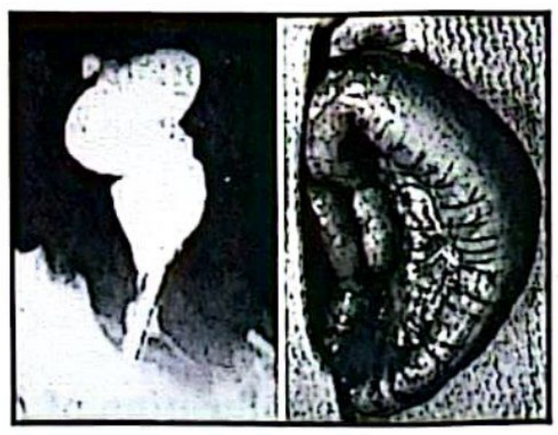


Fig: Hirschsprung disease showing constricted rectum and dilation of the sigmoid colon.

Malabsorption & Diarrhoea

Q. What is malabsorption syndrome? List five causes of malabsorption syndrome. (DU-16Ja,14Ju)

Q. Short note: Malabsorption syndrome. ***(For VIVA)***

Ans.

Malabsorption syndrome: Malabsorption is characterized by **defective absorption** of fats, fat- and water-soluble vitamins, proteins, carbohydrates, electrolytes and minerals, and water.

A hallmark of malabsorption is **steatorrhea**, characterized by excessive fecal fat and bulky, frothy, greasy, yellow or clay-colored stools.

Five important causes of malabsorption syndrome:

1. Pancreatic insufficiency
2. Celiac disease
3. Tropical sprue
4. Crohn disease
5. Cystic fibrosis
6. Primary bile acid malabsorption
7. Autoimmune enteropathy
8. Disaccharidase deficiency
9. Intestinal graft-versus-host disease *(after allogeneic hematopoietic stem cell transplantation)*.

Symptoms:

1. **General symptoms:**
   - Diarrhea, flatus, abdominal pain, weight loss, and muscle wasting
   - Anorexia, abdominal distention, and borborygmi

2. **Symptoms due to inadequate absorption of vitamins and minerals:**
   - Anemia and mucositis (due to pyridoxine, folate, or vitamin B_{12} deficiency)
   - Bleeding (due to vitamin K deficiency)
   - Osteopenia and tetany (due to calcium, magnesium, or vitamin D deficiencies)
   - Peripheral neuropathy (due to vitamin A or B_{12} deficiencies)
   - Endocrine and skin disturbances e.g. goiter and vitiligo (due to nutrient, micronutrient, and vitamin deficiencies).

(Ref: Robbins/10th/783)

Q. Define and classify diarrhoea.

Ans.

Diarrhoea: Diarrhoea is defined as an **increase in stool mass, frequency,** or **fluidity,** typically greater than 200 gm per day. In severe cases stool volume can exceed 14 L per day and, without fluid resuscitation, result in death.

(***N.B:*** Painful, bloody, small-volume diarrhea is known as **dysentery**.)

Both ***nutrient malabsorption*** and ***increased secretion of fluid by the intestine*** may contribute to diarrhea.

Classification of diarrhoea: Diarrhoea can be classified into **four** *major categories*-

1. **Secretory diarrhoea** is characterized by isotonic stool and persists during fasting.
2. **Osmotic diarrhoea,** such as occurs with lactase deficiency, is due to the excessive osmotic forces exerted by unabsorbed luminal solutes. The diarrhoea fluid is more than 50 mOsm more concentrated than plasma, and diarrhea abates with fasting.
3. **Malabsorptive diarrhoea** follows generalized failure of nutrient absorption, is associated with steatorrhea, and is relieved by fasting.
4. **Exudative diarrhoea** due to inflammatory disease is characterized by purulent, often bloody stools that continue during fasting.

(Ref: Robbins/10th/784)

Q. What is celiac disease?

Ans.

Celiac disease: Celiac disease (also known as **celiac sprue** or **glutensensitive enteropathy**) is an **immune-mediated disorder** triggered by the ingestion of **gluten-containing foods**, such as wheat, rye, or barley, in genetically predisposed individuals.

The malabsorptive diarrhea in celiac disease is due to ***loss of brush border surface area***, including villous atrophy, and, possibly, ***deficient enterocyte maturation*** as a result of ***immune-mediated epithelial damage***.

(Ref: Robbins/10th/784,787)

Q. Mention the differences between amoebic ulcer & ulcer of bacillary dysentery.

Ans.

Differences between amoebic ulcer & ulcer of bacillary dysentery:

Traits	Amoebic ulcer	Bacillary dysentery
1. Site in large intestine	Most common in proximal part	Most common in distal part
2. Basic change	Necrosis	Suppurative
3. Depth of ulcer	Usually deep	Usually swallow
4. Edge	Undermined (Flask-shaped)	Clear cut
5. Floor formed by	Muscularis mucosa, muscle coat or peritoneum	Submucosa coat (as it is swallow)
6. Intervening mucosa	Healthy	Inflammed
7. Trophozoites of *Entamoeba histolytica*	Present	Absent
8. Bacteria	Few normal flora	Gram-negative bacteria

Infectious Enterocolitis

Q. Write about pseudomembranous colitis.

Ans.

Pseudomembranous colitis: Pseudomembranous colitis is generally caused by ***Clostridioides*** (formerly ***Clostridium***) ***difficile*** and is also referred to as **antibiotic-associated colitis** or **antibiotic-associated diarrhea.**

(***N.B***: While other organisms such as *Salmonella, Clostridium perfringens* type A, or *Staphylococcus aureus* may also produce diarrhea in the context of antibiotic therapy, only *C. difficile* causes pseudomembranous colitis.)

This condition is morphologically distinguished by **superficial grayish mucosal exudates** consisting of necrotic, loosely adherent mucosal debris (***pseudomembrane***).

Cause: Overgrowth of **exotoxin-producing *Clostridium difficile.***

Risk factors: Risk factors for *C. difficile*–associated colitis include-

- Antibiotic treatment
- Advanced age
- Hospitalization
- Immunosuppression.

Clinical features: Individuals with *C. difficile*–associated colitis present with-

- Fever
- Leukocytosis
- Abdominal pain
- Cramps
- Watery diarrhea
- Dehydration.

Diagnosis: The diagnosis is usually made by **detection of *C. difficile* toxin**, rather than by culture, and is supported by the characteristic **histopathology**.

Morphology: Mucopurulent exudate that characteristically erupts from **damaged crypts** to form **"volcano" lesions** and coalesces to form **pseudomembranes.**

Treatment: Metronidazole and vancomycin.

(Ref: Robbins/10th/793; BRS Pathology/5th/237)

Q. Write about Whipple Disease.
Ans.

Whipple Disease: It is a rare, multi-visceral chronic disease characterized by macrophages loaded with ***Tropheryma whippelii*** organisms.

Clinical presentation: The clinical presentation of Whipple disease is usually a **triad** of diarrhea, weight loss, and arthralgia. Extraintestinal symptoms may precede malabsorption by months or years and include arthritis; arthralgia; fever; lymphadenopathy; and neurologic, cardiac, or pulmonary disease.

Morphologic features: Distinctive **PAS-positive macrophages** in intestinal mucosa; *Tropheryma whippelii* bacilli visualized by electron microscopy.

(Ref: Robbins/10th/794; Pathoma/2014/108; BRS Pathology/5th/234)

(N.B: Clinical symptoms occur because bacteria-laden macrophages accumulate within the small intestinal lamina propria and mesenteric lymph nodes, causing lymphatic obstruction. Thus, the malabsorptive diarrhea of Whipple disease is due to impaired lymph drainage.)

(Ref: Robbins/10th/794)

Irritable Bowel Syndrome (IBS)

Q. What do you mean by IBS? (SU-17M)
Ans.

Irritable Bowel Syndrome (IBS): Irritable bowel syndrome (IBS) is a ***functional gastrointestinal disorder*** characterized by chronic, relapsing abdominal pain, bloating, and changes in bowel habits.

The peak prevalence of IBS is between **20 and 40 years of age**, and there is a significant **female predominance.**

Types: It should be recognized that IBS is a syndrome and that multiple illnesses may be represented under this global descriptor. IBS is currently divided (as defined by successive revisions of the Rome criteria) into:

1. Diarrhea-predominant IBS
2. Constipation-predominant IBS
3. Mixed subtypes.

Diagnosis: Despite very real symptoms, the **endoscopic** and **microscopic evaluations** are **normal** in IBS patients. Thus, the ***diagnosis depends on clinical symptoms*** and ***functional testing***.

IBS is presently diagnosed using **clinical criteria** that require the occurrence of **abdominal pain** or **discomfort at least 3 days per month over 3 months** with improvement following defecation and a change in stool frequency or form.

(Ref: Robbins/10th/798)

Inflammatory Bowel Disease (IBD)

Q. What is inflammatory bowel disease? (DU-11Ju) **Describe the pathogenesis of inflammatory bowel disease.**

Q. Name the inflammatory bowel diseases (IBD). (DU-23M, RU-20M,12Ja)
Q. Short note: Inflammatory bowel diseases (IBD). (RU-17M,09Ja)
Ans.
Inflammatory bowel disease (IBD): Inflammatory bowel disease (IBD) is a **chronic condition** resulting from **complex interactions between intestinal microbiota** and **host immunity** in **genetically predisposed individuals** that leads to **inappropriate mucosal immune activation.**

(Ref: Robbins/10th/798)

The two disorders that comprise IBD are **ulcerative colitis** and **Crohn disease.**

Ulcerative colitis involves only the **colon and rectum** and is generally limited to the **mucosa and submucosa.** In contrast, **Crohn disease,** which has also been referred to as **regional enteritis** (because of frequent ileal involvement) may involve **any area of the GI tract** and is typically **transmural.**

(Ref: Robbins/10th/799)

Etiology and pathogenesis: IBD results from a ***combination*** of abnormalities in ***immune regulation, host-microbe interactions,*** and ***epithelial barrier functions*** in ***genetically susceptible individuals.***

The genetic and environmental elements that contribute to disease:

1. **Mucosal immunity:** A plethora of immune signaling and regulatory genes including those encoding HLA molecules and cytokines have been associated with IBD.
2. **Autophagy and cellular stress responses:** Genetic associations and molecular analyses indicate that defects in autophagy and cellular stress responses contribute to IBD pathogenesis.
3. **Host-microbial interactions:** The gut microbiome (composed of bacteria, fungi, and viruses) can modulate mucosal immunity. Conversely, the immune system can markedly alter the microbiome by mechanisms that include luminal secretion of antimicrobial peptides and antibacterial IgA. This interplay between microbes and the immune system may contribute to IBD pathogenesis.

(Ref: Robbins/10th/799)

Nice to Know:

Autophagy: *Autophagy is a normal homeostatic mechanism that clears damaged organelles and is upregulated in response to cellular stress including nutrient deprivation and endoplasmic reticulum stress.*

Autophagy is also a means of clearing sources of reactive oxygen species and intracellular pathogens.

(Ref: Robbins/10th/800)

Q. Why Crohn's disease & ulcerative colitis are considered idiopathic disease?
Ans.
Crohn's disease & ulcerative colitis are considered idiopathic disease: The basis of the abnormalities involved in the pathogenesis of IBD is still not established, that is why both ulcerative colitis & Crohn's disease are considered idiopathic disease.

Q. Write down morphology of Crohn's disease.
Q. Mention three important features of Crohn's disease. (DU-17Ja)
Q. Shot note: Crohn's disease. (SU-20M,09Ja)
Ans.
Crohn's disease: Crohn's disease is a form of ***inflammatory bowel disease,*** which has also been referred to as **regional enteritis,** commonly affects the **terminal ileum, ileocecal valve,** and **cecum** but may occur in **any area of the GI tract** from the **mouth to anus** and is typically **transmural.**

(Ref: Robbins/10th/799,800)

Pathogenesis: The prime culprits appear to be T cells particularly CD4+ T cells and their products. Crohn's disease appears to be the results of **delayed type hypersensitivity reaction** induced by IFN-γ & TNF-α produced by T_H^1 cells.

Clinical features:

A. Intestinal manifestations:

- Non-bloody diarrhoea, fever, abdominal pain
- Weight loss
- Iron deficiency anemia
- Fibrosing strictures
- Fistulae
- Perforations
- Peritoneal abscesses.

B. Extra-intestinal manifestations:

- Migratory polyarthritis
- Uveitis
- Sarcoiliitis
- Ankylosing spondylitis
- Erythema nodosum
- Cutaneous granulomas
- Clubbing of the fingertips
- Pericholangitis
- Primary sclerosing cholangitis.

Morphology:

Macroscopic:

- **Site of involvement:** Any portion of the GI tract (from mouth to anus), but the most common sites are ***terminal ilium*** and ***colon***.
- **Distribution:** Multiple, separate, sharply delineated areas **(skip lesion)**.
- **Wall:** Inflammation occurs in ***all layers***, down to the serosa. This predisposes to ***strictures***, ***fistulas*** and ***adhesions***.
- **Lumen:** The lumen is narrowed which appears on X-ray as **'string sign'.** The mucosa shows **'serpiginous ulcers'**, while intervening surviving mucosa is swollen giving **'cobblestone appearance'**.
- **Mesenteric fat:** Frequently extends around the serosal surface **(creeping fat).**

Microscopic:

- **Non-caseating granulomas** (a **hallmark of Crohn disease**)
- **Transmural** infiltration of ***chronic inflammatory cells*** (lymphocytes, plasma cells and macrophages)
- Distortion of mucosal architecture with ***loss of crypt epithelium***
- ***Patchy ulceration*** (which may take the form of deep fissures)
- ***Epithelial metaplasia***.

(Ref: Robbins/10th/800; Lecture SSMC)

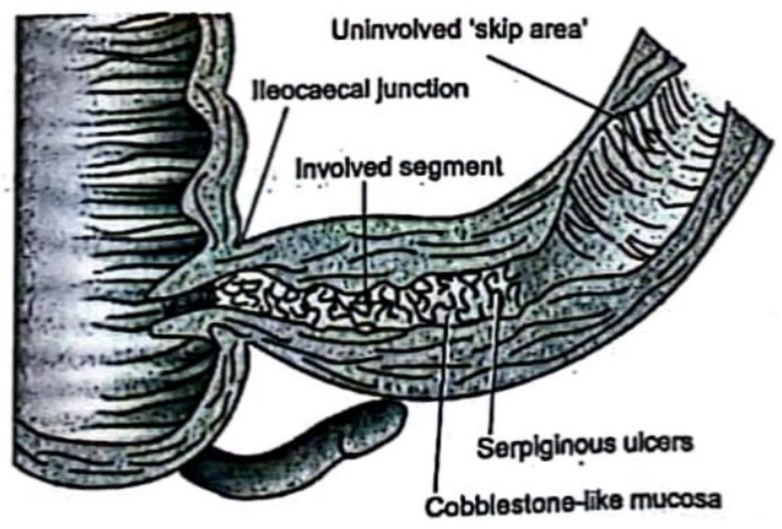


Fig: Crohn's disease of the terminal ileum.
(Ref: Robbins/10th/801; Harsh Mohan/7th/548; Lecture SSMC)

Q. Shot note: Ulcerative colitis.

Ans.

Ulcerative colitis: Ulcerative colitis is a severe ulcerating ***inflammatory bowel disease*** that is **limited to the colon** and **rectum** (most common site) and is generally limited to the **mucosa** and **submucosa.**

(Ref: Robbins/10th/799,801)

Clinical features:

A. Intestinal manifestations:
- Bloody diarrhoea with stringy mucoid material
- Urgency
- Tenesmus
- Lower abdominal pain and cramps that are temporarily relieved by defecation.

B. Extra-intestinal manifestations:
- Migratory polyarthritis
- Uveitis
- Sarcoiliitis
- Ankylosing spondylitis
- Skin lesions (e.g. pyoderma gangrenosum)
- Pericholangitis
- Primary sclerosing cholangitis.

(***N.B:*** **Arthritis** is the ***most common extra-intestinal feature*** in both **Crohn disease** and **ulcerative colitis.**)

Morphology:

***Macroscopic*:**
- **Continuous involvement** of rectum and colon **without any uninvolved skip areas**
- Red, raw colonic mucosa that bleeds easily
- Mucosa shows ***linear and superficial ulcers***, with preservation of adjacent mucosa which has the appearance of polyps (**'pseudopolyps'**), and the tips of these polyps may fuse to create **mucosal bridges**
- Chronic disease may lead to ***mucosal atrophy*** with a smooth mucosal surface that lacks normal folds Unlike Crohn disease, ulcerative colitis is **not transmural,** as a result-
  - Colonic wall is not thickened
  - Serosal surface is normal
  - Strictures do not occur

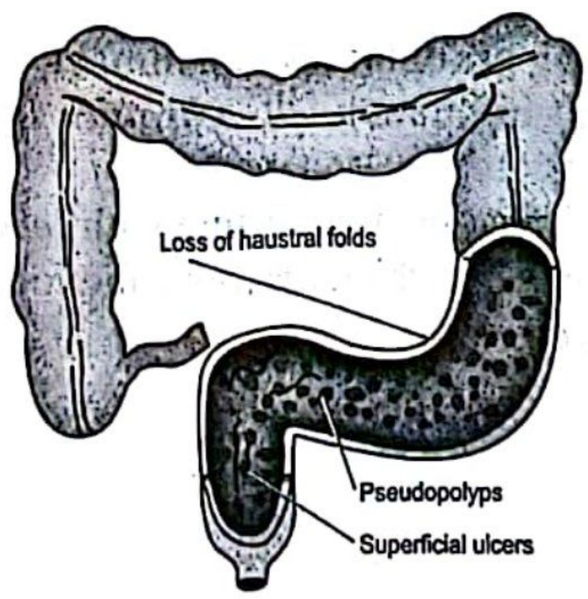


Fig: Ulcerative colitis.

***Microscopic*:**
- Diffuse inflammation limited to the mucosa and superficial submucosa
- Inflammatory infiltrates in lamina propria
- Crypt abscesses
- Crypt distortion
- Pseudopyloric epithelial metaplasia
- Depletion of goblet cells and mucin from gland epithelium
- Granulomas are not present.

(Ref: Robbins/10th/801-803; Harsh Mohan/7th/548; Lecture DMC, MMC)

Q. What are the differences between Crohn's disease and ulcerative colitis? (DU-23M,17Nv,14/13/11Ju,06M, BUP-22Nv/M,20Nv/M,19/18M,16Ja, RMU-23/22/21M,19/18/17Nv, 16Ju,13/12/08Ja, CU-20Ju,19/18M, SU-17M,16Ja)
Q. Write down 4 differences between Crohn's disease and ulcerative colitis. (DU-17Ja)
Q. Write the morphological differences between Crohn's disease and ulcerative colitis. (DU-16Ja)
Q. Write 4 microscopic differences between Crohn's disease and ulcerative colitis. (CMU-22M)
Q. List most important macroscopic and microscopic differences between Crohn's disease and ulcerative colitis. (DU-17M)
Ans.

Differences between Crohn's disease and ulcerative colitis: ***(Very Important for VIVA)***

Features	Crohn's disease	Ulcerative colitis
MACROSCOPIC		
Bowel region	Ileum ± colon	Colon only
Distribution	Skip lesions	Diffuse (without skip areas)
Stricture	Yes	Rare
Wall appearance	Thick	Thin
MICROSCOPIC		
Depth of inflammation	Transmural	Limited to mucosa & submucosa
Ulcers	Deep, knife-like	Superficial, broad-based
Pseudopolyps	Rarely seen	Commonly seen
Lymphoid reaction	Marked	Moderate
Fibrosis	Marked	Mild to none
Serositis	Marked	Mild to none
Granulomas	Yes (~35%)	No
Fistulae/sinuses	Yes	No
CLINICAL		
Perianal fistula	Yes (in colonic disease)	No
Fat/vitamin malabsorption	Yes	No
Malignant changes	Rare	Frequent (in long-standing cases of >10 years duration)
Recurrence after surgery	Common	No
Toxic megacolon	No	Yes

(***N.B***: All features may not be present in a single case).

(Ref: Robbins/10th/799; Harsh Mohan/7th/552; Lecture SSMC)

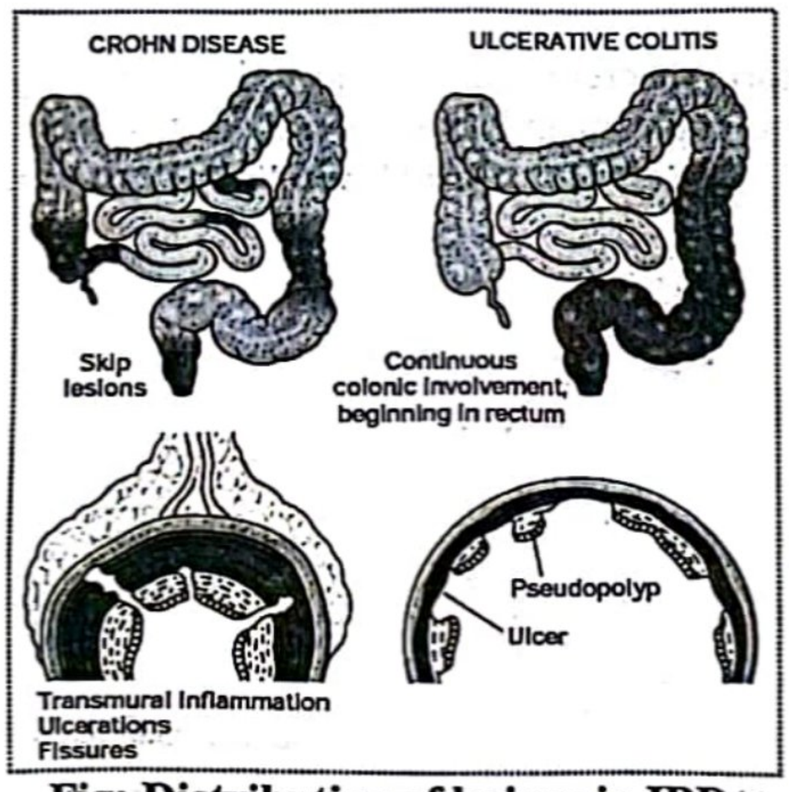


Fig: Distribution of lesions in IBD.

Tumors of Intestine

Q. Mention the possible sites of metastasis of malignant tumor of small intestine. (DU-04M)

Ans.

Possible sites of metastasis of malignant tumor of small intestine:

1. Regional lymph nodes
2. Peritoneal cavity
3. Liver
4. Lung
5. Bones
6. Brain.

Q. Short note: Carcinoid tumour. (DU-03Ja, SU-14Ju) ***(For VIVA)***

Ans.

Carcinoid tumor: The term **carcinoid** is named as the tumor resembles a ***carcinoma-like lesion***, but with a much more indolent clinical course.

It is the **malignant proliferation of neuroendocrine cells**. Although characteristically slow growing, these tumors are of **low-grade malignancy** and may metastasize.

When metastatic to the **liver**, neuroendocrine tumors can lead to **carcinoid syndrome** which is caused by the elaboration of vasoactive peptides and amines, especially **serotonin**.

Sites:

1. Appendix } (most common)
2. Terminal ileum
3. Rectum
4. Colon
5. Stomach, duodenum, esophagus
6. Lungs
7. Gallbladder
8. Meckel's diverticulum.

Morphology:

***Gross/macroscopic*:**

- Small, polypoid or plateau-like elevations rarely more than 3 cm in diameter.
- Overlying mucosa may be intact or ulcerated.
- A solid, yellow-tan appearance on transcetion.

***Microscopic*:**

- Neoplastic cells may form discrete islands, trabeculae, stands, glands, or undifferentiated sheets.
- A scant, pink granular cytoplasm and a round to oval stippled nucleus.

(Ref: Robbins/7th/866,867; Pathoma/2014/108; Harsh Mohan/7th/560)

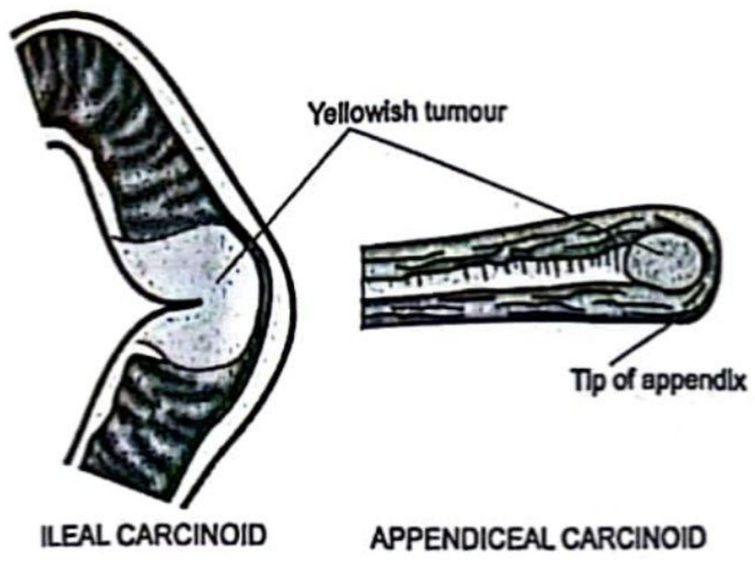


Fig: Carcinoid tumour. Gross appearance at common locations in longitudinal section.

Q. Short note: Carcinoid syndrome. (CU-09Ja) ***(For VIVA)***

Ans.

Carcinoid syndrome: The term **'carcinoid syndrome'** refers to the systemic symptoms produced when vasoactive substances (**serotonin**) enters into systemic circulation from the carcinoid tumour.

Mechanism: Metastasis of carcinoid tumour to the liver allows **serotonin** to bypass liver metabolism. Serotonin is released into the hepatic vein and leaks into systemic circulation via hepato-systemic shunts, resulting in **carcinoid syndrome.**

Clinical features:

(a) Cutaneous flushing
(b) Watery diarrhea and abdominal cramps
(c) Bronchospasm
(d) Valvular lesions of the right side of the heart.

Symptoms can be triggered by **alcohol** or **emotional stress,** which stimulate **serotonin** release from the tumour.

(Ref: Robbins/7th/868; Pathoma/2014/109; BRS Pathology/5th/235; Harsh Mohan/7th/560)

Q. Mention important predisposing factors for colorectal carcinoma.
Q. What are the risk factors of colorectal carcinoma?
Q. Mention the clinical features of colorectal carcinoma.

Ans.

Colorectal carcinoma: Colorectal carcinoma (adenocarcinoma) is the **most common malignancy of the GI tract.** This represent nearly 15% of all cancer related deaths, and is second only to lung cancer.

Predisposing factors for colorectal carcinoma:

1. **Age:** Incidence peaks at 60 to 70 years of age, and fewer than 20% of cases occur before age 50.
2. **Sex:** Males are affected slightly more often than female.
3. **Dietary factors:**
   - Low intake of unabsorbable vegetable fiber
   - High intake of refined carbohydrates and fat
4. **Geographic variations**
5. **Obesity**
6. **Physical inactivity**
7. **Pre-existing adenomas**
8. **Hereditary non-polyposis colonic cancer (HNPCC or Lynch syndrome)**
9. **Other factors**
   - Inflammatory bowel disease (especially ulcerative colitis)
   - Diverticular disease for long duration
   - Tobacco smoking

Clinical features of colorectal carcinoma:

1. Occult bleeding (melaena)
2. Change in bowel habits, more often in left-sided growth
3. Abdominal pain
4. Loss of weight (cachexia)
5. Loss of appetite (anorexia)
6. Anaemia, weakness, malaise.

(Ref: Robbins/10th/813; Harsh Mohan/7th/587)

Q. Mention role of diatery factors for causation of colon cancer. (RU-13Ju)

Ans.

Role of diatery factors for causation of colon cancer: The dietary factors most closely associated with increased colorectal cancer rates are-

- Low intake of unabsorbable vegetable fiber and
- High intake of refined carbohydrates and fat.

Although these associations are clear, the mechanistic relationship between diet and risk remains poorly understood. However, it is theorized that reduced fiber content leads to decreased stool bulk and altered composition of the intestinal microbiota. This change may increase synthesis of potentially toxic oxidative by-products of bacterial metabolism, which would be expected to remain in contact with the colonic mucosa for longer periods of time as a result of reduced stool bulk.

Deficiencies of vitamins A, C, and E, which act as free-radical scavengers, may compound damage caused by oxidants. High fat intake enhances the hepatic synthesis of cholesterol and bile acids, which can be converted into carcinogens by intestinal bacteria.

(Ref: Robbins/10th/814)

Q. Write down the pathogenesis of colorectal carcinoma. (CMU-21M)

Ans.

Pathogenesis of colorectal carcinoma:

1. **APC mutation/β-catenin mechanism:**
   - ***Loss of tumour suppressor APC*** (adenomatous polyposis coli) **gene** (80% cases of sporadic colon cancer). Since the function of *APC* gene is linked to β-catenin, loss of *APC* gene results in translocation of β-catenin to the nucleus where it activates transcription of other genes, mainly *MYC* and cyclin D1, both of which stimulate cell proliferation.
   - ***Point mutation in K-RAS gene*** follows loss of *APC* gene (seen in 10 to 50% cases of adenoma-carcinoma).
   - ***Deletion of DCC gene*** (60-70% cases of colon cancer).
   - ***Loss of p53 tumour suppressor gene*** (70-80% cases of colon cancer).
2. **Microsatellite instability (MSI) mechanism:** This pathway accounts for 10-15% cases of colon cancer. Basic mutation is loss of DNA repair gene. This results in a situation in which repetitive DNA sequences (i.e. microsatellites) become unstable during replication cycle, termed microsatellite instability (MSI), which is the hallmark of this pathway.

(Ref: Harsh Mohan/7th/588)

Intestinal Polyp

Q. Define polyp. (CU-18M) **Name the polyps of gastrointestinal tract.** (DU-13Ju)
Q. Classify intestinal polyp. (CMU-21/19Nv,18Nv/M,15Ju/Ja,13Ja, RU-13Ju)
Q. What are the polyps of small intestine? (RU-20M)
Q. Short note: Polyp. ***(Very Important for VIVA)***

Ans.

Polyp: A polyp is a tumourous mass that protrudes into the lumen of the gut.

(Ref: Robbins/10th/807)

Or,

A polyp is a descriptive term for any elevation of the intestinal surface.

(Ref: BRS Pathology/5th/238)

Polyps are **most common** in the **colon** but may occur in the esophagus, stomach, or small intestine.

Types of polyps:

1. **Non-neoplastic polyps:**
   - Hyperplastic polyp *(commonest)*

- Inflammatory polyp
- Hamartomatous polyp
  a) Juvenile polyps
  b) Peutz-Jeghers polyps

2. **Neoplastic (adenomatous) polyps:** They are true **neoplasms** rather than benign proliferations of tissue. They are usually **asymptomatic** but can result in rectal bleeding. This includes-

- Tubular adenoma *(most common type - 75%)*
- Tubulovillous adenoma
- Villous adenoma
- Sessile serrated adenoma.

(Ref: Robbins/10th/807; BRS Pathology/5th/238)

Q. Short note: Villous adenoma. (DU-16Ju)

Ans.

Villous adenoma: Villous adenoma is a type of **adenomatous polyp** that grows in the colon and other places in the gastrointestinal tract and sometimes in other parts of the body. They account for approximately 10% of adenomatous polyps.

Morphology: Villous adenomas are large sessile tumour with velvety surface, and are characterized by large numbers of fingerlike villi.

Fig: Villous adenoma with long, slender projections that are reminiscent of small intestinal villi.

Malignant potential: They have the **highest potential** for malignancy of all of the adenomatous polyps; they become malignant in more than 30% of cases.

(Ref: Robbins/10th/810; BRS Pathology/5th/238,239)

Nice to Know:

Familial adenomatous polyposis (FAP): Familial adenomatous polyposis (FAP) is an autosomal dominant disorder in which patients develop numerous colorectal adenomas as teenagers. It is caused by somatic mutations of the adenomatous polyposis coli, or ***APC*** **gene.**

(Ref: Robbins/10th/812)

Hereditary non-polyposis colorectal cancer (HNPSS): HNPCC is caused by inherited mutations in mismatch repair genes that encode proteins responsible for the detection, excision, and repair of errors that occur during DNA replication. HNPCC, also known as **Lynch syndrome,** was originally described based on familial clustering of cancers at several sites, including the colorectum, endometrium, stomach, ovary, ureters, brain, small bowel, hepatobiliary tract, pancreas, and skin. HNPCC is thought to account for 2% to 4% of all colorectal cancers, making it the most common syndromic form of colon cancer. Colon cancers in HNPCC patients tend to occur at younger ages than sporadic colon cancers and are often located in the right colon.

(Ref: Robbins/10th/813)

The Appendix

Q. Give the aetio-pathogenesis of acute appendicitis. *(Important for VIVA)*

Ans.

Etiology of acute appendicitis: In 50-80% of cases, acute appendicitis is associated with overt luminal obstruction, usually caused by-

1. A small stone-like mass of stool, or fecalith
2. Gall stone
3. Any tumour in the oppening of appendix e.g. benign polyp.
4. Mass of worms e.g. *Oxyuriasis vermicularis*.

Pathogenesis of acute appendicitis:

Obstruction of the lumen of the appendix due to any cause
↓
After obstruction mucous secretion within appendix increases and accumulation within it
↓
Increase intraluminal pressure that presses over the wall
↓
As a result, venous obstruction leading to ischaemia and venous congestion
↓
Proliferation of microbial agents causing inflammation
↓
Additional inflammatory oedema and exudates further embarrass the blood supply
↓
More injury
↓
Acute appendicitis
↓
If the process is not stopped there will be aggravation of the state leading to gangrenous necrosis.

(Ref: Robbins/10th/819)

Q. Describe the morphology of acute appendicitis with possible complications. (DU-03S)

Q. What are the complications of acute appendicitis? (RMU-22Nv)

Ans.

Morphology of acute appendicitis:

***Macroscopic*:**

- Appendix is swollen and distended
- Serosal covering is reddened
- Cut section shows the lumen filled with pus
- Mucosa shows ulceration and foci of suppurative necrosis

***Microscopic*:**

- Subserosal vessels are congested.
- Infiltration of acute inflammatory cells (neutrophil) throughout the mucosa, sub-mucosa, and muscularis propria
- Ulcerations are also present within the mucosa
- Muscle fibres are separated by oedema fluid

Complications of acute appendicitis:

1. Appendicular lump
2. Appendicular abscess
3. Perforation / Burst appendix
4. Gangrene of the appendix
5. Peritonitis (generalized / systemic)

6. Pyelophlebitis
7. Portal venous thrombosis
8. Liver abscess
9. Bacteraemia
10. Pelvic abscess
11. Subphrenic abscess.

(Ref: Robbins/10th/819)

Q. Name the tumours of the appendix. ***(Very Important for VIVA)***

Ans.

Tumours of the appendix:

- Neuroendocrine (carcinoid) tumor (most common)
- Adenoma
- Adenocarcinoma
- Mucinous cystadenoma
- Mucinous cystadenocarcinoma.

(Ref: Robbins/10th/819)

Q. Short note: Pseudomyxoma peritoneii. ***(Very Important for VIVA)***

Ans.

Pseudomyxoma peritoneii: In mucinous cystadenocarcinoma, presence of invasion of appendicular wall by malignant neoplastic cells and spread beyond appendix as peritoneal implants. The peritoneal cavity becomes distended with tenacious, semisolid mucin, a condition called ***pseudomyxoma peritoneii.***

(Ref: Robbins/10th/819)

Q. A 18 years old male presented with colicky pain in the right iliac fossa along with fever and vomiting. (CMU-21Nv)

a) What is your clinical diagnosis?

b) What are the possible causes of it?

c) What are the laboratory tests and positive findings to establish the diagnosis?

Ans.

Clinical diagnosis: Acute appendicitis.

Possible causes of acute appendicitis: *Please write from above.*

Laboratory tests with positive findings to establish the diagnosis: *Please write from above.*

Q. A man of 20 years presented with acute abdominal pain, vomiting and fever. On examination, tenderness was observed in his right iliac fossa. His blood picture shows neutropenic leukocytosis. What is your clinical diagnosis? After operation what do you expect in the histopathology of the involved organ? (DU-15Ja)

Ans.

Clinical diagnosis: Acute appendicitis.

Expected histopathological findings of the appendix: *Please write from above.*

Q. Name the different diseases of GIT. (DU-18Ja)

Ans.

Diseases of GIT: *Please write from above the diseases of oral cavity, esophagus, stomach & intestine.*

CHAPTER 07

LIVER AND BILIARY TRACT

Diseases of the Liver

Q. Name the diseases of liver.
Q. Name important pathologic lesions of liver.
Q. Classify hepatic tumours. (CU-15Ja, RU-12Ju)
Q. List the neoplasms of liver. (RMU-22M,21Nv)
Ans.

Important pathologic lesions of liver:

1. **Liver failure:**
   - Acute liver failure
   - Chronic liver failure and cirrhosis
   - Portal Hypertension
   - Acute-on-chronic liver failure
2. **Infectious disorders:**
   - Viral hepatitis
     - ***Hepatotrophic viruses*** (hepatitis A, B, C, D & E)
     - ***Non-hepatotrophic viruses*** (EBV, CMV, HSV, adenovirus, and yellow fever virus)
   - Bacterial, fungal, and parasitic infections
3. **Autoimmune hepatitis**
4. **Drug- and toxin-induced liver injury**
5. **Fatty liver disease:**
   - Alcoholic liver disease
   - Nonalcoholic fatty liver disease (NAFLD)
6. **Inherited liver disease:**
   - Haemochromatosis
   - Wilson disease
   - α_1-antitrypsin deficiency
7. **Cholestatic disease:**
   - Physiologic jaundice of the newborn

- Hereditary hyperbilirubinemia
- Cholestasis of sepsis
- Primary hepatolithiasis
- Neonatal cholestasis
- Autoimmune cholangiopathies
  - Primary biliary cholangitis (PBC)
  - Primary sclerosing cholangitis (PSC)

8. Circulatory disorders:

- Portal vein obstruction & thrombosis
- Hepatic vein thrombosis (Budd-Chiary syndrome)

9. Hepatic disease associated with pregnancy:

- Pre-eclampsia & eclampsia
- Acute fatty liver of pregnancy
- Intrahepatic cholestasis of pregnancy.

10. Tumors: *(Very Important for VIVA)*

A) Benign:

- Cavernous haemangioma
- Hepatocellular adenoma

B) Malignant:

- ***Primary:***
  - Hepatoblastoma (childhood tumour)
  - Hepatocellular carcinoma (HCC) (adenocarcinoma)
  - Intrahepatic cholangiocarcinoma
  - Combined hepatocellular-cholangiocarcinoma
  - Angiosarcoma
  - Epithelioid hemangioendothelioma
  - Primary hepatic lymphoma (non-Hodgkin lymphoma)
- ***Metastatic*** (more common than primary)**:** Virtually any cancer in any site of the body may spread to the liver. The most common primary sources are-
  - Colon
  - Breast
  - Lung
  - Pancreas
  - Leukemias, melanomas, and lymphomas.

(Ref: Robbins/10th/822-872)

Q. Name some major primary diseases of liver. *(For VIVA)*

Ans.

Major primary diseases of liver:

1. Viral hepatitis
2. Alcoholic liver disease
3. Non-alcoholic fatty liver disease (NAFLD)
4. Hepatocellular carcinoma (HCC).

(Ref: Robbins/10th/822-872; Lecture SSMC)

Q. Mention the patterns of hepatic injury.

Ans.

Patterns of hepatic injury:

1. **Reversible injury:** These include **accumulation of fat** (steatosis) and **bilirubin** (cholestasis), as well as ballooning, a change marked by **cell swelling, cytoplasmic clearing,** and **clumping of intermediate filaments,** which when prominent, may form ***Mallory hyaline.***
2. **Irreversible injury:** When injury is irreversible, hepatocytes may die by **necrosis** or **apoptosis.**

(Ref: Robbins/10th/824)

Q. Name the inflammatory liver diseases. (DU-04Ja)
Q. What are the causes of hepatitis? (RMU-21M)
Ans.
Inflammatory liver diseases:

A. Infectious disorders:

1. **Viral hepatitis**
   - *Hepatotrophic viruses* (hepatitis A, B, C, D & E)
   - *Non-hepatotrophic viruses* (EBV, CMV, HSV, adenovirus, and yellow fever virus – often in association with systemic infection)
2. **Bacterial infections**
   - *Staphylococcus aureus*
   - *Salmonella typhi*
   - *T. pallidum*
   - *Bartonella henselae*
   - *M. tuberculosis*
3. **Parasitic and helminthic infections**
   - Malaria
   - Schistosomiasis
   - Strongyloidiasis
   - Cryptosporidiosis
   - Leishmaniasis
   - Echinococcosis
   - Liver flukes - *Fasciola hepatica, Opisthorchis* species, and *Clonorchis sinensis*
   - Hydatic cyst by echinococcal infection
   - Liver abscess by amebic and other protozoal and helminthic infections
4. **Fungal infections**
   - Histoplasmosis
   - Candidiasis

B. Autoimmune hepatitis.

(Ref: Robbins/10th/823-839)

Liver Failure

Q. Mention the clinical features and complications of liver failure.
Q. Short note: Liver failure.
Ans.
Liver failure: The **most severe** form of liver disease is **liver failure,** which may be **acute** (due to sudden and massive hepatic destruction) or (more commonly) **chronic,** following years of insidious, progressive liver injury.

In some cases, individuals with chronic liver disease develop ***acute-on-chronic liver failure,*** in which an unrelated **acute injury is superimposed on late-stage chronic disease** or there is a **"flare" of the chronic disease** that leads to liver decompensation.

Whatever the sequence, **80% to 90% of functional capacity must be lost** before hepatic failure appears.

Clinical features:

1. Jaundice
2. Hypoalbuminemia *(peripheral edema)*
3. Hyperammonemia *(cerebral dysfunction)*
4. Fetor hepaticus *(body odor "musty" or "sweet and sour")*
5. Palmar erythema *(a reflection of local vasodilatation)*
6. Spider angiomas of the skin
7. In male - hypogonadism and gynecomastia.

Complications:

1. Coagulopathy
2. Hepatic encephalopathy
3. Portal hypertension
4. Bleeding esophageal varices
5. Hepatorenal syndrome
6. Portopulmonary hypertension.

(***N.B***: When the liver can **no longer maintain homeostasis,** ***liver transplantation*** offers the best **hope for survival;** without transplantation, the **mortality rate** in persons with hepatic failure is **about 80%.**)

(Ref: Robbins/10th/826,831)

Q. Define acute liver failure. (CU-15Ju)

Q. Mention some causes of acute liver failure.

Ans.

Acute liver failure: Acute ('fulminant') liver failure is defined as an acute liver illness associated with encephalopathy and coagulopathy that occurs within 26 weeks of the initial liver injury in the absence of pre-existing liver disease.

(Ref: Robbins/10th/826)

Causes of acute liver failure: ***Mnemonic*** for causes of acute liver failure:

- **A:** Acetaminophen, hepatitis A, autoimmune hepatitis
- **B:** Hepatitis B
- **C:** Hepatitis C, cryptogenic
- **D:** Drugs/toxins, hepatitis D
- **E:** Hepatitis E, esoteric causes (Wilson disease, Budd-Chiari syndrome)
- **F:** Fatty change of the microvesicular type (fatty liver of pregnancy, valproate, tetracycline, Reye syndrome).

(Ref: Robbins/10th/831)

Rare causes of acute liver failure include **abnormalities of blood flow, metabolic disorders,** and **malignancies,** most commonly leukemia or lymphoma (33%), followed by breast cancer (30%) and colon cancer (7%). An etiology cannot be established in about 15% of adult and 50% of pediatric cases.

(Ref: Robbins/10th/826)

Q. Mention the clinical features and complications of acute liver failure. ***(For VIVA)***

Ans.

Clinical features and complications of acute liver failure:

1. Nausea, vomiting, and jaundice
2. Marked elevation of serum liver transaminases
3. Initial liver enlargement followed by shrinkage
4. Cholestasis – manifested by yellow discoloration of the skin and sclera (jaundice and icterus, respectively)
5. Hepatic encephalopathy

6. Clotting factors deficiencies and coagulopathy - manifested by easy bruisability, life-threatening or fatal intracranial bleeding, disseminated intravascular coagulation (DIC) etc.
7. Portal hypertension (although it is more commonly seen with chronic liver failure)
8. Hepatorenal syndrome
9. Progressive multiorgan system failure (and, if transplantation is not possible, death ensues).

(Ref: Robbins/10th/826)

Q. What do you mean by hepatic encephalopathy? (DU-18M,16Ju)

Q. Short note: Hepatic encephalopathy. ***(Very Important for VIVA)***

Ans.

Hepatic encephalopathy: Hepatic encephalopathy is a spectrum of disturbances in consciousness, ranging from subtle behavioral abnormalities, to marked confusion and stupor, to deep coma and death.

It may progress over days, weeks, or months following acute hepatic injury.

(Ref: Robbins/10th/827)

Associated fluctuating neurologic signs:

- **Rigidity** and **hyperreflexia.**
- **Asterixis / flapping tremor** (a particularly characteristic sign, which is manifested as nonrhythmic, rapid extension-flexion movements of the head and extremities, best seen when the arms are held in extension with dorsiflexed wrists).

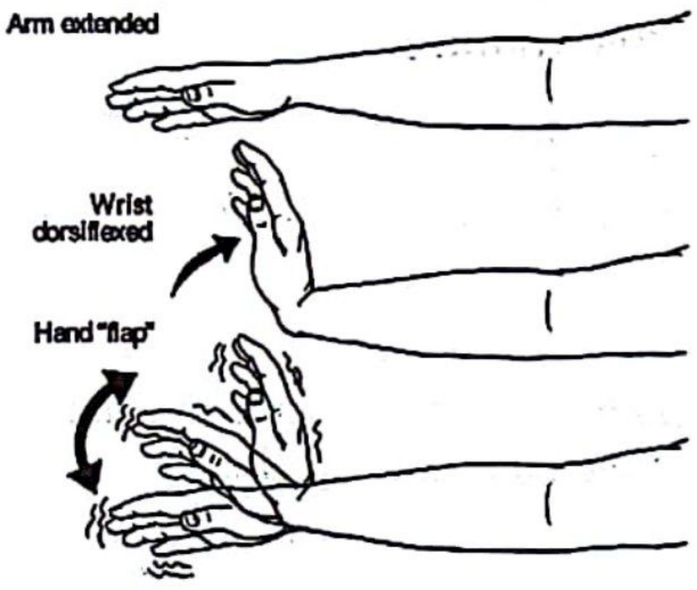


Fig: Asterixis / flapping tremor.

Pathogenesis: Hepatic encephalopathy is believed to be caused by **elevated ammonia levels**, which correlate with impaired neuronal function and cerebral edema.

The principal source of the ammonia is the **gastrointestinal tract**, where it is produced by **microorganisms** and also by **enterocytes** during glutamine metabolism. Normally, ammonia is transported in the portal vein to the liver, where it is metabolized in the **urea cycle**; in severe liver disease, this detoxification mechanism fails.

(Ref: Robbins/10th/827)

Q. What do you mean by hepatorenal syndrome? ***(Very Important for VIVA)***

Ans.

Hepatorenal syndrome: It is a form of **renal failure** occurring in individuals with **liver failure** in whom there is no intrinsic morphologic or functional cause for kidney dysfunction.

The syndrome's onset is marked by a drop in urine output and increasing levels of urea and creatinine in the blood.

Sodium retention, impaired free-water excretion, and decreased renal perfusion and glomerular filtration rate are the main renal functional abnormalities.

The decline in renal function is **reversible** if liver function is **restored**, for example, by **liver transplantation.**

(Ref: Robbins/10th/827)

Nice to Know: ***(Very Important for VIVA)***

The leading causes of **chronic liver failure** worldwide include **chronic hepatitis B, chronic hepatitis C, non-alcoholic fatty liver disease,** and **alcoholic liver disease.**

(Ref: Robbins/10th/828)

Chronic Liver Disease (CLD) and Cirrhosis of Liver

Q. Define chronic liver disease. (CU-15Ja)

Ans.

Chronic liver disease (CLD): Chronic liver disease (CLD) or chronic hepatitis represents a series of liver disorders of varying causes and severity in which hepatic inflammation and necrosis continue for **at least 6 months.**

Or,

Chronic liver disease (CLD) or chronic liver injury is defined as hepatic injury, inflammation and/or fibrosis occurring in the liver for **more than 6 months**

(Ref: Davidson's/23rd/856)

Q. Define cirrhosis of liver. (DU-22/17M,13Ju,12Ja, BUP-22Nv,21Nv/M, RMU-22Nv,21/20/19M, 18/17Ja,15Ju, 14Ja,12/11Ju,10Ja, CU-19M,15Ju,05Ja, SU-06Ja) ***(V.V.I for VIVA)***

Ans.

Cirrhosis of liver: Cirrhosis may be defined as the **end-stage of chronic liver disease** which is characterized by-

1. **Bridging fibrous septae** in the form of delicate bands or broad scars linking portal tracts with one another and portal tracts with terminal hepatic veins
2. **Parenchymal nodules** containing proliferating hepatocytes encircled by fibrosis, with diameters varying from very small (<0.3 cm, micronodules) to large (several cm, macronodules)
3. **Disruption of the architecture of the entire liver.**

(Ref: Robbins/8th/837)

Or,

Cirrhosis (*end-stage chronic liver disease*) is a condition marked by **diffuse remodeling** of the liver into **parenchymal nodules** (often regenerative) surrounded by **fibrous bands** and a variable degree of **vascular** (often portosystemic) **shunting.**

(Ref: Robbins/10th/828)

Cirrhosis is characterized by **diffuse hepatic fibrosis** and **nodule formation.**

(Ref: Davidson's/23rd/856)

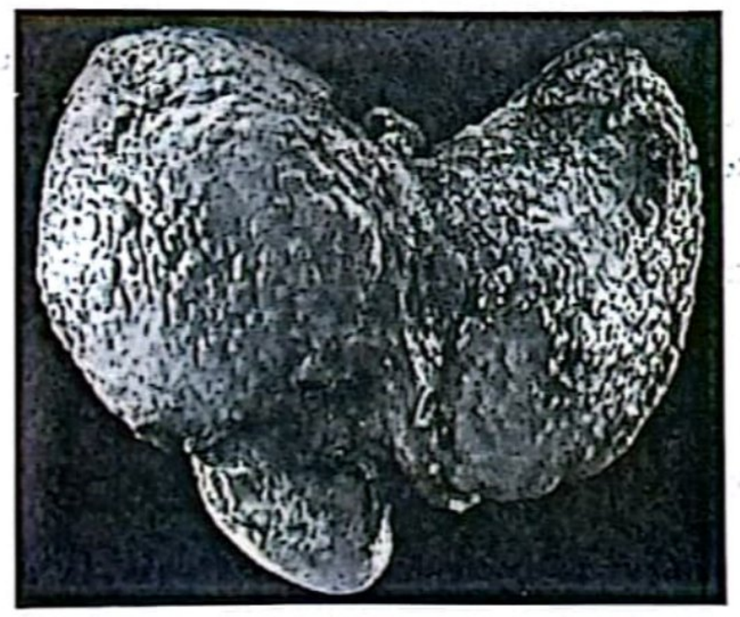


Fig: Cirrhosis resulting from chronic viral hepatitis.

(***N.B*:** Although **cirrhosis** and **chronic liver failure** are often associated, they are **not synonymous**; not all cirrhosis leads inexorably to chronic liver failure, and not all end-stage chronic liver disease is cirrhotic.)
(Ref: Robbins/10th/828)

Q. Classify cirrhosis of liver. (RU-20M,17/14Ja,12/11Ju,10Ja, SU-06Ja)
Q. Mention the types of liver cirrhosis. (RU-15Ju)
Ans.

Classification of cirrhosis of liver: ***(Important for VIVA)***

***Etiological classification*:**

1. **Alcoholic liver disease:** (60-70%), common in Western country
2. **Viral hepatitis:** Chronic HBV & HCV infection - 10% (***most common in Bangladesh***)
3. **Biliary cirrhosis:** 5 - 10%
4. **Primary haemochromatosis:** 5%
5. **Wilson disease:** Rare
6. **α_1-antitrypsin deficiency:** Rare
7. **Cryptogenic cirrhosis:** 10 - 15% *(where cause is not found)*
8. **Drug induced cirrhosis:** e.g. α-methyldopa
9. **Cardiac cirrhosis:** Due to long standing heart failure.

***Morphological classification*:**

1. **Macronodular:** Characterized by larger nodules of various sizes (size is > 3 mm in diameter), e.g. cirrhosis due to viral hepatitis.
2. **Micronodular:** Characterized by small nodules (size is < 3 mm in diameter), e.g. alcoholic cirrhosis (initially), biliary cirrhosis, pigment cirrhosis etc.
3. **Mixed:** Both macro and micronodules are found, e.g. alcoholic cirrhosis (late).

(Ref: Robbins/10th/828 + 7th/883)

Q. Mention the causes / risk factors of cirrhosis of liver / chronic liver failure. (DU-18M,16/13Ju, RMU-23M,20Nv,18M/Ja, CMU-23/21M, BUP-22Nv,21Nv/M, SU-20M)
Q. What are the common causes of cirrhosis of liver? (DU-10Ja, RU-18M, CU-06S)
Q. Mention 4 important causes of cirrhosis in Bangladesh. (DU-07Ja)
Q. A male of 25 years presented with mild jaundice, gynaecomastia, testicular atrophy & ascites. Give your probable diagnosis. Mention 5 important causes of this condition. (DU-15Ja)
Ans.

Probable diagnosis: Cirrhosis of liver.

Causes of liver cirrhosis:

1. Chronic viral hepatitis (B or C) – (most common cause in Bangladesh)
2. Alcohol - (common in Western country)
3. Non-alcoholic fatty liver disease (NAFLD)
4. Immune:
   - Primary sclerosing cholangitis
   - Autoimmune hepatitis
5. Biliary:
   - Primary biliary cirrhosis (PBC)
   - Secondary biliary cirrhosis
   - Cystic fibrosis
6. Genetic:
   - Haemochromatosis
   - Wilson's disease
   - α1-antitrypsin deficiency

7. Cryptogenic cirrhosis (unknown – 15%)
8. Chronic venous outflow obstruction
9. Any chronic liver disease.

(Ref: Robbins/10th/828; Davidson's/23rd/866)

Q. Describe briefly the pathogenesis of cirrhosis of liver. (CMU-21Nv,20Nv/M,18Nv/M,17M, 06S,05Ja, BUP-21Nv/M, SU-20M, RU-19/18M)

Q. Write the mechanism of cirrhotic death. (DU-10Ja)

Ans.

Pathogenesis of cirrhosis of liver: The central pathogenic processes in cirrhosis are ***death of hepatocytes***, ***extracellular matrix (ECM) deposition***, and ***vascular reorganization***.

Chronic inflammation of liver

↓

Inflammatory cytokines (e.g. TNF, lymphotoxin, TGF-β, IL-1 and platelet derived growth factor) are produced by stimulated Kupffer cell, endothelial cells, hepatocytes and bile duct epithelium.

↓

Causes transformation of **ITO cells (peri-sinusoidal stellate cells)** into **myofibroblast like cells (*collagen-secreting cells*)**

↓

Collagen deposition (type-I & III) in the space of Disse, creating fibrotic septal tracts

↓

The vascular architecture of the liver is disrupted by the parenchymal damage and scarring

↓

Continued deposition of collagen in the space of Disse is accompanied by the loss of fenestrations of sinusoidal endothelial cells

↓

Eventual fibrosis

↓

Remaining hepatocytes stimulated to regenerate

↓

Proliferate as spherical nodules within the confines of fibrous septa

↓

So, there is fibrosis, loss of architecture and formation of regenerative nodules

↓

Cirrhosis of liver.

(Ref: Robbins/10th/828)

Q. Why there is jaundice in cirrhosis?

Ans.

Jaundice in cirrhosis: Disruption of the interface between the parenchyma and portal tracts may also ***obliterate biliary channels***, leading to the development of jaundice.

(Ref: Robbins/9th/828)

Q. Discuss the pathology / morphology of cirrhosis of liver. (DU-04Ja, BUP-21Nv/M, CU-15Ju/Ja, RU-04M,03Ja)

Ans.

Pathology / morphology of liver cirrhosis:

***Macroscopic*:**

a. Liver is enlarged in the early stage.
b. In late stage liver becomes smaller because of loss of cell and fibrous contraction.
c. Liver is much firmer than normal.
d. Nodularity is the most characteristic feature.

***Microscopic*:**

a. Loss of normal liver architecture.
b. Regenerative nodules are found within fibrous band.
c. Enlargement of liver cells with atypical nuclei.
d. The vasculature of liver is greatly distorted.
e. The fibrous bands obstruct the portal venous radicles leading to abnormal communication between portal vein and hepatic arteriole.

(Ref: Robbins/10th/828)

Q. Enumerate the clinical features of cirrhosis of liver. (RU-07Ju)
Ans.

Clinical features of cirrhosis of liver:

1. **Features of portal hypertension:**
   a. Splenomegaly
   b. Ascites & edema
   c. Collateral vessel formation (e.g. Caput medusae)
   d. Variceal bleeding (e.g. esophageal, gastric & rectal varices)
   e. Fetor hepaticus (results from portosystemic shunting of blood)

2. **Features of hepatic insult:**
   a. **Jaundice**
   b. **Ascites**
   c. **Circulatory changes**
      - Spider nevae / spider angioma / spider telangiectasia of the skin
      - Palmar erythema (a reflection of local vasodilation)
      - Cyanosis

   d. **Endocrine changes**
      - ↓ Libido
      - ↓ Body hair } (in both male and female)
      - **In male:**
        - Gynaecomastia
        - Testicular atrophy
        - Impotence
      - **In female:**
        - Breast atrophy
        - Menstrual abnormality
        - Amenorrhoea

e. Haemorrhagic tendency
- Bruises
- Purpura
- Epistaxis

f. Hepatic (portosystemic) encephalopathy

g. Other features
- Pruritus (itching)
- Pigmentation
- Clubbing of fingers and toes
- Dupytren's contracture.

(Ref: Davidson's/23rd/867; Robbins/10th/828; Lecture SSMC)

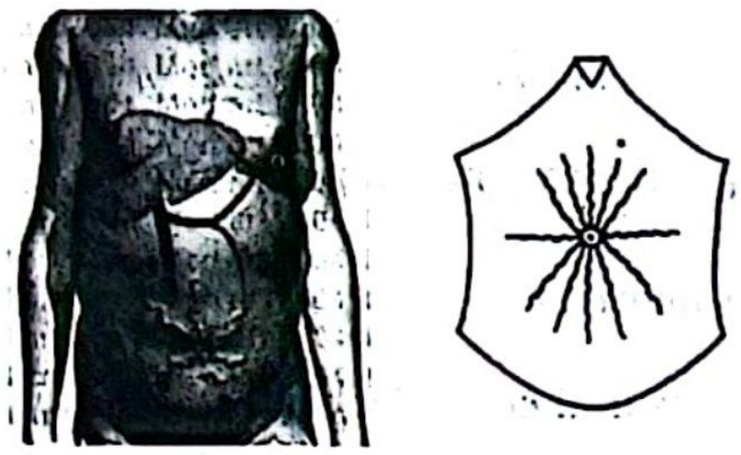


Fig: Caput medusae.

(N.B: Spider telangiectasia, gynaecomastia and parotid enlargement are most common in alcoholic cirrhosis.)

(Ref: Davidson's/23rd/867)

(N.B: Spider nevae / spider angioma / spider telangiectasia is a central, pulsating, dilated arteriole from which small vessels radiate.)

(Ref: Robbins/10th/828)

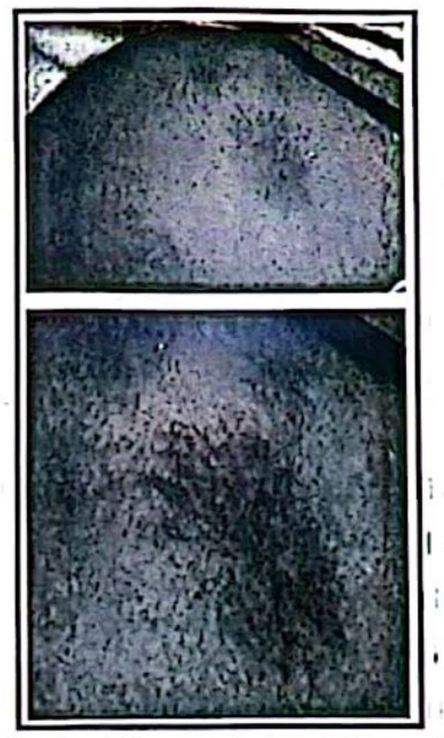


Fig: Spider telangiectasia.

Q. Enumerate the complications of cirrhosis of liver. (RU-21/20M,07Ju)
Q. Mention the complications of cirrhosis of liver. (DU-12Ja, RU-19/18/17M,15Ju,14Ja,11Ju)
Q. Write down the mechanism of cirrhotic death. (DU-10Ja)
Q. Mention the features of chronic liver failure / 'decompensated liver disease' / end stage liver disease. (V.V.I. for VIVA)

Ans.

Complications / causes of death in cirrhosis of liver (features of chronic liver failure / 'decompensated liver disease' / end stage liver disease):

1. Jaundice
2. Ascites
3. Hepatic encephalopathy
4. Bleeding from esophageal varices
5. Hepato-renal syndrome
6. Hepato-pulmonary syndrome
7. Spontaneous bacterial peritonitis (SBP)
8. Development of hepatocellular carcinoma.

(Ref: Davidson's/23rd/867; Robbin's/10th/828; Harsh Mohan/7th/588)

*(**N.B:** Chronic liver failure develops when the metabolic capacity of the liver is exceeded.)*

Q. Short note: Cirrhosis of liver. (SU-22/19Nv, CU-11Ja,08Ju)

Ans.

Cirrhosis of liver: *Please write from above.*

Q. Short note: Hepatotrophic virus and complications of cirrhosis of liver. (RU-16Ju)

Ans.

Hepatotrophic viruses: *Please write from below.*

Complications of cirrhosis of liver: *Please write from above.*

Q. Define ascites. What are the causes of ascites?

Q. Enumerate the important causes of ascites. (DU-21Oct/M)

Ans.

Ascites: Ascites refers to the **accumulation of excess fluid in the peritoneal cavity.**

In 85% cases ascites is caused by **cirrhosis.** It usually becomes clinically detectable when **at least 500 ml** have accumulated.

(Ref: Robbins/10th/829)

Causes of ascites:

Exudative (high protein)	▪ Malignancy ▪ Tuberculosis ▪ Acute pancreatitis ▪ Hypothyroidism
Transudative (low protein)	▪ Liver cirrhosis ▪ Renal failure (including nephrotic syndrome) ▪ Congestive heart failure ▪ Hypoproteinaemia: - Protein-losing enteropathy - Malnutrition ▪ Hepatic venous occlusion (Budd–Chiari syndrome) ▪ Meigs' syndrome ▪ Constrictive pericarditis

(Ref: Davidson's/23rd/847,862; Robbins/10th/829; Lecture SSMC)

Q. Write down the mechanism of formation of ascites in cirrhosis of liver. (DU-18M,16/13Ju, CMU-23M)

Q. Describe briefly the pathogenesis of ascites in cirrhosis of liver. (DU-18M,16/13Ju)

Q. How ascites is developed in cirrhosis of liver? (DU-22Nv,12/09Ja, RU-09Ja, SU-06Ja)
Q. How ascites develop in cirrhosis & chronic liver disease? (DU-15Ju, RU-10Ja)
Ans.
Mechanism of ascites in liver cirrhosis:

1. **Splanchnic vasodilatation:** Cirrhosis (fibrosis) of liver → Pronounced splanchnic vasodilatation → Falling of systemic arterial pressure → Reduced renal blood flow → Activation of the renin–angiotensin system with secondary hyperaldosteronism → ↑ Na^+ and H_2O retention by the kidney → ↑ Plasma hydrostatic pressure → ↑Transudation of fluid into the peritoneal cavity → Ascites.

2. **Percolation of hepatic lymph into the peritoneal cavity** (lymph formation exceeds lymph return)**:** Cirrhosis → Hepatic lymphatic flow (20 L/day in exchange of normal 800-1000 ml/day) exceeding thoracic duct lymph return capacity → Percolation of excess amount of hepatic lymph (rich in proteins) into the peritoneal cavity → Ascites.

3. **Intestinal fluid leakage:** Cirrhosis of liver → Portal hypertension → Increased perfusion pressure in intestinal capillaries → Movement of additional fluid out of intestinal capillaries into the abdomen → Ascites.

4. **Secondary hyperaldosteronism:** Cirrhosis of liver → Impaired hepatic metabolism of aldosterone → ↑ Aldosterone → Increased Na^+ and H_2O retention by the kidney → Increased plasma hydrostatic pressure → Increased transudation of fluid into the peritoneal cavity → Ascites.

5. **Hypoalbuminaemia:** Cirrhosis of liver → Impaired function of liver → Decreased synthesis of albumin → Hypoalbuminaemia → Decreased plasma oncotic pressure → Transudation of fluid into the peritoneal cavity → Ascites.

(Ref: Robbins/10th/829; Davidson's/23rd/863)

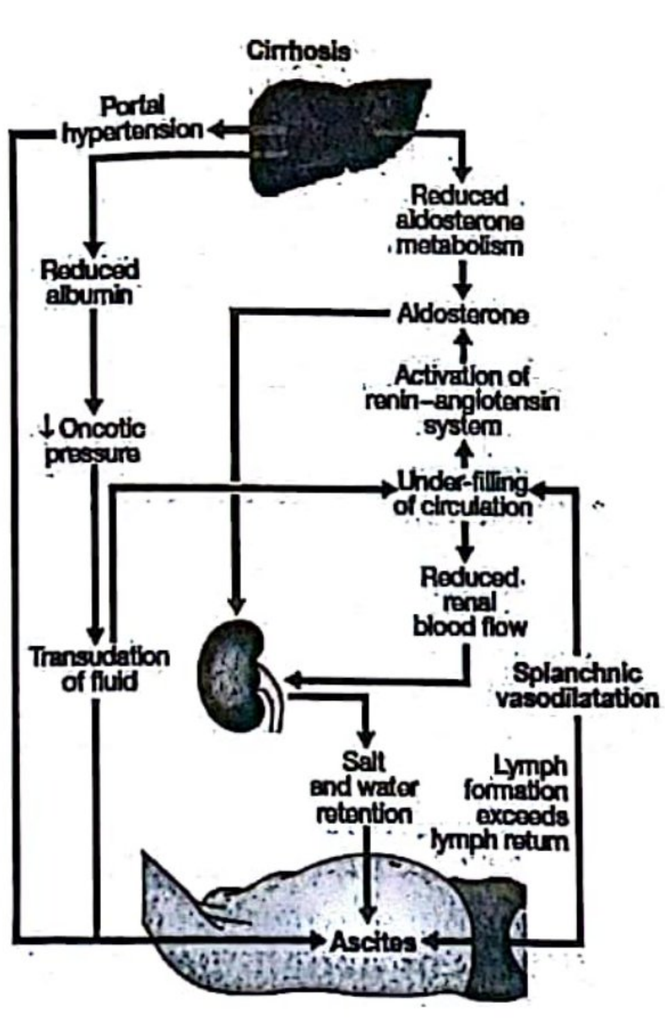


Fig: Pathogenesis of ascites in cirrhosis.

Q. Why hypoproteinemic edema occurs in cirrhosis of liver? (RU-07Ja)
Ans.
Hypoproteinemic edema occurs in cirrhosis of liver: Liver is the principal site of protein (mainly albumin) synthesis. In cirrhosis, the normal architecture of liver is altered. There is degeneration and intracellular accumulation in the liver. The hepatocytes undergo necrosis and apoptosis. So, protein (albumin) synthesis is decreased. Plasma oncotic pressure is decreased. As a result hypoproteinemic edema occurs.

(Ref: Robbins/10th/829; Davidson's/23rd/863)

Q. A male of 25 years presented with mild jaundice, gynaecomastia, testicular atrophy and ascites. Give your probable diagnosis. Mention five important etiology for this condition. (DU-15Ja)

Ans.

Diagnosis: Liver cirrhosis.

Etiology: *Please write from above.*

Q. A male of 50 years with a past history of jaundice presents with hepatomegaly and edema. Histopathology of liver shows loss of architecture, formation of parenchymal nodules and fibrosis. What is your diagnosis? What are the causes for development of edema in this patient? (DU-15Ju)

Ans.

Diagnosis: Cirrhosis of liver.

Causes of edema (ascites) in the patient of cirrhosis: *Please see above.*

Q. A male of 40 years had a history of jaundice 6 months back. Now he has developed distension of abdomen with gynaecomastia and hemorrhoid. What is the likely diagnosis? Name the liver function tests that are expected to be altered. (DU-12Ju)

Ans.

Diagnosis: Liver cirrhosis.

Liver function tests that are expected to be altered in cirrhosis of liver:

a. Serum bilirubin – Increased
b. Prothrombin time (PT) – Prolonged
c. Serum albumin – Low.

Q. A male 35 years has presented with ascites and splenomegaly. His blood is HBsAg positive. He has a needle biopsy done of his liver. What is the likely diagnosis?

Ans.

Diagnosis: Liver cirrhosis.

Hepatomegaly

Q. Name common pathological conditions of hepatomegaly. (DU-04M)

Ans.

Causes of hepatomegaly:

A. Hepatic causes:

1. Viral hepatitis
2. Liver abscess (pyogenic and amoebic)
3. Primary hepatocellular carcinoma (hepatoma)
4. Secondaries in the liver (liver metastasis)
5. Polycystic liver
6. Hydatid cyst
7. Cirrhosis (early): non-alcoholic fatty liver disease, alcohol, haemochromatosis
8. Amyloidosis
9. Hepatic vein outflow obstruction (Budd Chiari syndrome).

B. Other causes:

1. Chronic malaria
2. Chronic kala-azar
3. Leukaemia
4. Lymphoma
5. Congestive cardiac failure (CCF)
6. Chronic constrictive pericarditis
7. Typhoid fever.

(Ref: Davidson's/23rd/862; Medicine Lecture SSMC; ABM Abdullah/4th/145)

Q. What are the causes of tender hepatomegaly? ***(Very Important for VIVA)***

Ans.

Causes of tender hepatomegaly:

- Acute viral hepatitis
- Congestive cardiac failure (CCF)
- Liver abscess
- Hepatocellular carcinoma
- Chronic constrictive pericarditis.

(Ref: Medicine Lecture SSMC; ABM Abdullah/4th/146)

Nice to Know:

Budd Chiari syndrome: The **obstruction** of two or more major **hepatic veins** produces **liver enlargement, pain,** and **ascites,** a condition known as **Budd Chiari syndrome.**

(Ref: Robbins/10th/862)

Portal Hypertension

Q. What are the causes of portal hypertension?

Ans.

Causes of portal hypertension: Increased resistance to portal blood flow may develop in a variety of circumstances, which can be divided into *prehepatic intrahepatic, and posthepatic:*

1. **Prehepatic causes:**
   - Obstructive thrombosis of portal vein
   - Structural abnormalities such as narrowing of the portal vein before it ramifies in the liver
2. **Intrahepatic causes:**
   - Cirrhosis from any cause
   - Nodular regenerative hyperplasia
   - Primary biliary cirrhosis (even in the absence of cirrhosis)
   - Schistosomiasis
   - Massive fatty change
   - Diffuse, fibrosing granulomatous disease (e.g., sarcoid)
   - Infiltrative malignancy, primary or metastatic
   - Focal malignancy with invasion into portal vein (particularly hepatocellular carcinoma)
   - Amyloidosis
3. **Posthepatic causes:**
   - Severe right-sided heart failure
   - Constrictive pericarditis
   - Hepatic vein outflow obstruction.

(Ref: Robbins/10th/828,829)

Q. What are the complications / clinical consequences of portal hypertension? (RU-18Ja)
Ans.

Clinical consequences of portal hypertension: The four major clinical consequences of portal hypertension are-

1. Ascites
2. Formation of porto-systemic venous shunts-
   - Hemorrhoids
   - Esophageal varices
   - Periumbilical caput medusae
3. Congestive splenomegaly
4. Hepatic encephalopathy.

(Ref: Robbins/10th/829)

Hepatitis

Q. What are the causes of hepatitis? (DU-05Ja, RMU-22Nv,21M)
Ans.

Causes of hepatitis: ***(V.V.I for VIVA)***

A) Infections:

1. **Viral:**
   - ***Hepatotrophic viruses*** - Hepatitis viruses (A, B, C, D, and E). *(HBV & HCV cause hepatocellular carcinoma).*
   - ***Non-hepatotropic viruses*** - Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), adenovirus, and yellow fever virus (often in association with systemic infection).
2. **Bacterial:** *Staphylococcus aureus*, *Salmonella typhi*, *T. pallidum*.
3. **Parasitic and helminthic:** Malaria, schistosomiasis, strongyloidiasis, cryptosporidiosis, leishmaniasis, echinococcosis, infections by liver flukes *Fasciola hepatica* and *Clonorchis sinensis*, amebiasis.

B) Autoimmune hepatitis

C) Drugs: e.g. acetaminophen, isoniazid, α-methyldopa, methotrexate etc.

D) Toxin: e.g. mushroom poisoning (afla toxin).

E) Alcohol: e.g. chronic alcoholism.

F) Metabolic: e.g. non-alcoholic fatty liver disease, haemochromatosis, Wilson disease, α_1-antitrypsin deficiency, neonatal hepatitis.

G) Cholestasis: Biliary stricture, sclerosing cholangitis.

H) Congestion: Congestive cardiac failure (CCF), Budd-Chiari syndrome.

(Ref: Robbins/10th/831)

Q. What do you mean by hepatotrophic viruses? Why they are named so?
Q. Enumerate hepatotrophic viruses. (RU-17Nv) ***(Very Important for VIVA)***
Ans.

Hepatotrophic viruses: Hepatotrophic viruses are the group of viruses (hepatitis A, B, C, D, and E) that have a specific affinity for the liver.

(Ref: Robbins/10th/831)

Nice to Know:

Hepatitis A virus: Hepatitis A virus (HAV) infection is a **self-limited disease** and **does not lead to chronic hepatitis** or a **carrier state.**

HAV is **spread** by ingestion of contaminated water and foods, and is endemic in countries with poor hygiene and sanitation. In high income countries, sporadic infections may be contracted by the consumption of raw or steamed shellfish (oysters, mussels, clams), which concentrate the virus from seawater contaminated with human sewage. Sexual transmission may occur, but maternal-fetal transmission does not. Since HAV viremia is transient, blood-borne transmission of HAV is rare, and donated blood is not screened for this virus.

The **incubation period** for HAV is 2 to 6 weeks.

Affected individuals have nonspecific **symptoms** such as fatigue and loss of appetite, and they often develop jaundice.

Most patients **recover** within 3 months, and disease resolution occurs in nearly all patients by 6 months. Acute liver failure occurs in 0.1% to 0.3% of patients, especially those with chronic liver disease due to another etiology. Other uncommon **complications** include prolonged cholestasis and relapse of disease within 6 months of the original onset.

Extrahepatic manifestations include rash, arthralgia and immune complex mediated complications like leukocytoclastic vasculitis, glomerulonephritis and cryoglobulinemia.

HAV **vaccine** is effective in preventing infection.

(Ref: Robbins/10th/831)

Q. Give the possible outcome of hepatitis-B virus infection. *(Very Important for VIVA)*

Ans.

Possible outcome of hepatitis-B virus infection:

1. Acute hepatitis followed by recovery and clearance of the virus (99% cases of acute hepatitis turn to recovery)
2. Death from fulminant hepatitis (<1% cases)
3. Chronic hepatitis with or without progression to cirrhosis
4. Hepatocellular carcinoma
5. An asymptomatic, "healthy" carrier state

(Ref: Robbins/10th/832; Park/23rd/215)

(***N.B:*** Patients with long-standing ***HBV***- or ***HCV***-related cirrhosis are at **increased risk** for the development of **hepatocellular carinoma**.)

(Ref: Robbins/10th/838)

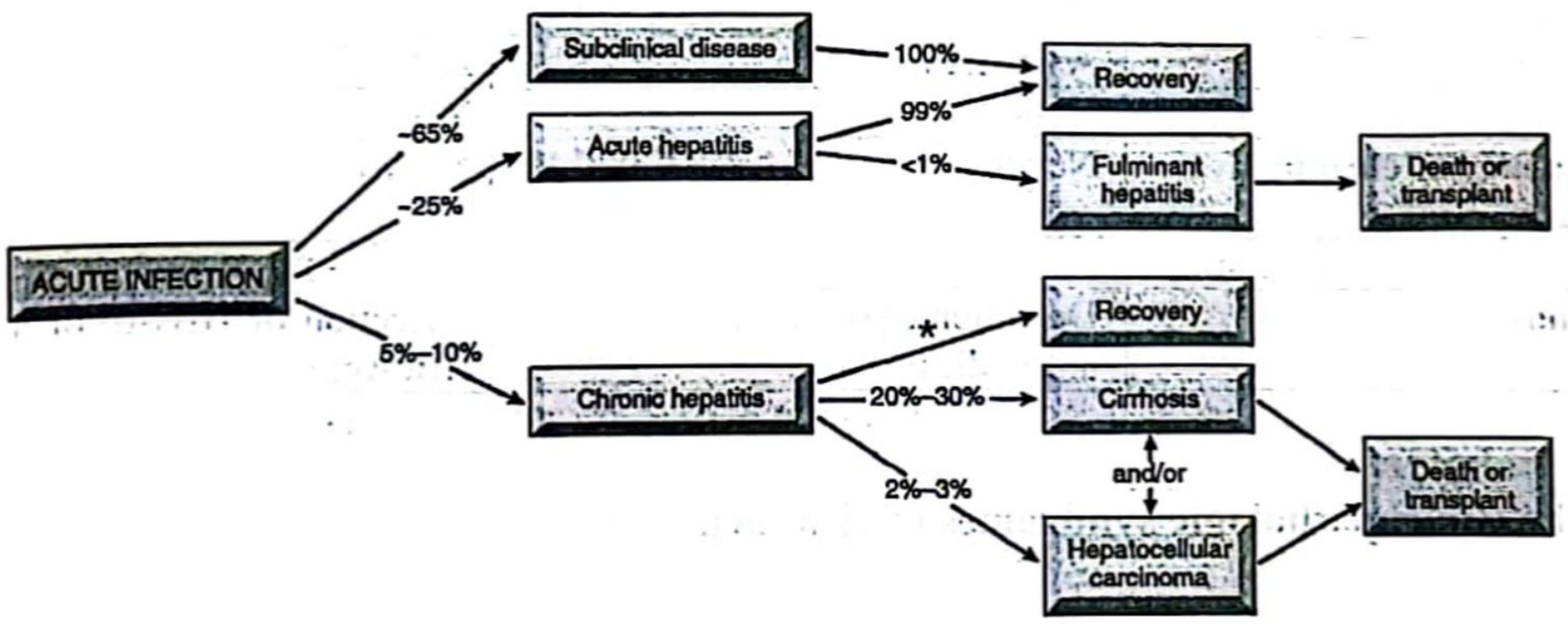


Fig: Potential outcomes of hepatitis B infection in adults.

Q. What is fulminant hepatitis / fulminant liver failure? *(Very Important for VIVA)*

Ans.

Fulminant hepatitis / fulminant liver failure: Very rapid onset acute liver failure is referred to as **"fulminant liver failure"** and is typically the result of ***massive hepatic necrosis*** which is most often induced by **drugs** or **toxins.**

Causes of fulminant liver failure:

- Accidental or deliberate ingestion of acetaminophen (Paracetamol) - accounts for almost 50% of adult cases
- Autoimmune hepatitis
- Other drugs/toxins
- Acute hepatitis A, B, and E infections.

(Ref: Robbins/10th/826)

Q. Mention the serologic markers of HBV infection. (RU-03Ja)

Ans.

Serologic markers of HBV infection: *(Very Important for VIVA)*

a. ***Antigen*:**
   - HBsAg
   - HBeAg

b. ***Antibody*:**
   - Anti-HBc IgM
   - Anti-HBs IgM
   - Anti-HBe IgM.

(Ref: Robbins/10th/833)

Q. Mention the differences between hepatitis-A and hepatitis-B viruses.

Ans.

Differences between hepatitis-A and hepatitis-B virus:

Traits	Hepatitis-A virus	Hepatitis-B virus
1. Type of virus	Single stranded RNA virus (ssRNA)	Partially double stranded DNA virus (dsDNA)
2. Viral family	Hepatovirus; related to picornavirus	Hepadnavirus
3. Route of transmission	Faeco-oral (contaminated food or water)	Parenteral, sexual contact, perinatal
4. Mean incubation period	2 - 6 weeks	2 to 26 weeks (mean 8 weeks)
5. Age group	Children	All age
6. Antigens	HAAg	HBsAg, HBcAg, HBeAg
7. Antibody	Anti-HAV	Anti-HBs
8. Carrier state	None	Yes
9. Frequency of chronic liver disease	Never	5%-10%
10. Hepatocellular carcinoma	No	Yes
11. Diagnosis	Detection of serum IgM antibodies	Detection of HBsAg or antibody to HBcAg; PCR for HBV DNA

(Ref: Robbins/10th/831,832,836)

Q. Give the clinicopathologic syndromes of viral hepatitis.

Ans.

Clinicopathologic syndromes of viral hepatitis: Major features of the main clinicopathologic syndromes associated with viral hepatitis are as follows-

(1) Acute asymptomatic infection with recovery.
(2) Acute symptomatic infection (anicteric or icteric) with recovery.
(3) Acute liver failure with massive to submassive hepatic necrosis (10% of cases).
(4) Chronic hepatitis (*hepatic disease for more than 6 months*), with or without progression to cirrhosis
(5) Carrier state.

(Ref: Robbins/10th/836,837)

Nice to Know:

HAV and **HEV** (in immunocompetent hosts) **do not cause chronic hepatitis,** and only a small number of HBV-infected adult patients develop chronic hepatitis. In contrast, HCV is notorious for progressing to chronic infection.

Acute liver failure is unusual and is seen primarily with **HAV, HBV**, or **HDV** infection, depending on region. **HEV** can cause **acute liver failure** in **pregnant women. HBV** and **HCV** are responsible for most cases of **chronic hepatitis.**

(Ref: Robbins/10th/837)

Q. Write down the morphologic changes in acute hepatitis. (CU-19M)
Q. Mention the microscopic features in liver in acute viral hepatitis. (DU-17M)
Ans.

Morphology of liver in acute viral hepatitis:

Macroscopic:

- **In mild acute viral hepatitis:** Liver may be normal in size, or enlarged (due to inflammation).
- **Acute viral hepatitis associated with acute liver failure and massive liver necrosis:** Liver may be shrunken.

Microscopic:

- **Portal** and **lobular inflammatory infiltrate** comprised predominantly of **lymphocytes** and variably admixed with **plasma cells** and **eosinophils.**
- **Hepatocyte injury** may result in **necrosis** or **apoptosis,** often with **pigmented macrophages** scavenging the **dead cell debris.**
- Necrosis of groups of hepatocytes (i.e. **confluent necrosis**) may be seen in severe cases and can progress to necrosis of the entire lobule (i.e. **panlobular** or **panacinar necrosis**) or connect vascular structures (i.e. **bridging necrosis**).
- **Liver failure** can develop with **massive hepatic necrosis.**

(Ref: Robbins/10th/837)

Q. Give the pathogenesis and fate of chronic active hepatitis. (DU-05Ja)
Q. Discuss briefly chronic viral hepatitis with their complications. (DU-04M)
Q. Give morphology of chronic viral hepatitis. (SU-12Ju)
Q. Mention the microscopic features in liver in chronic viral hepatitis. (DU-17M)
Q. Mention complications of chronic hepatitis. (RU-17Nv)
Ans.

Chronic hepatitis: Chronic viral hepatitis is defined as symptomatic, biochemical or serological evidence of continuing or relapsing hepatic disease for **more than 6 months.**

(Ref: Robbins/10th/837)

Causes of chronic hepatitis:

1. Hepatitis viruses: HBV, HCV, and HBV+HDV
2. Chronic alcoholism

3. Wilson disease
4. α_1-antitrypsin deficiency
5. Drugs: Isoniazid, α-methyldopa, methotrexate
6. Autoimmunity.

Pathogenesis:

1. Continued loss of hepatocytes due to marked inflammatory infiltrate in portal tract & also into hepatic parenchyma
2. Progressive fibrosis.

Morphology:

***Macroscopic*:** Liver architecture is usually well preserved.

***Microscopic*:**

- Mononuclear portal infiltration.
- The inflammatory cells often cross the limiting plate and lead to injury of periportal hepatocytes (interface activity).
- This may be accompanied by a variable degree of lobular inflammation.
- Fibrosis develops with increasing liver damage manifesting initially as portal and periportal fibrosis.
- Fibrous septa develop and lead to portoportal bridging fibrosis, and eventually cirrhosis.

Clinical features (signs & symptoms):

1. Fatigue
2. Malaise
3. Loss of appetite
4. Occasional bouts of mild jaundice
5. Spider angiomas
6. Palmar erythema
7. Mild hepatomegaly
8. Vasculitis, glomerulonephritis, and cryoglobulinemia (in chronic HBV and HCV infection)

Liver function tests:

- Persistent elevation of serum transaminases (ALT/AST)
- Prolongation of the prothrombin time (PT)
- Hyperglobulinemia
- Hyperbilirubinemia
- Mild elevations in alkaline phosphatase level

Complications:

1. Cirrhosis of liver
2. Hepatocellular carcinoma.

(Ref: Robbins/10th/837)

Q. Mention the serological markers of chronic hepatitis. (RU-08Ja)

Ans.

Serological markers of chronic hepatitis:

1. **Hepatitis B:**
   - HBsAg - positive
   - Anti-HBc IgM - positive
   - Anti-HBe IgM - positive
2. **Hepatitis C:** Anti-HCV IgM & IgG Ab.
3. **Hepatitis D:** Anti-HDV IgM & IgG Ab.

(Ref: Lecture SSMC)

Q. Write down the serological markers of different types of viral hepatitis. (RU-05Ju)

Ans.

Serological markers of different types of viral hepatitis:

	HAV	HBV	HCV	HDV	HEV
Antigens	HA Ag	HBsAg HBeAg HBV DNA	Hepatitis C viral RNA (PCR)	Delta (D) Ag	-
Antibodies	Anti-HAV IgM & IgG	Anti HBc Anti HBs Anti HBe	Anti-HCV	Anti-HDV IgM & IgG	Anti HEV

(Ref: Lecture SSMC)

Q. What alteration will occur in liver function test in acute viral hepatitis? (DU-17M)

Ans.

Alterations will occur in liver function test in acute viral hepatitis:

- Serum bilirubin: *High*
- ALT & AST: *Very high*
- Alkaline phosphatase: *Slightly high*
- Viral markers: *Positive.*

Q. What is carrier state of hepatitis?

Ans.

Carrier state of hepatitis: A **"carrier"** is an individual who harbors and can transmit an organism, but has no symptoms.

For hepatotropic viruses, carrier state has been used to describe two separate scenarios:

(1) Individuals who harbor the virus but have no liver disease

(2) Individuals who harbor the virus and have asymptomatic nonprogressive liver damage.

In both cases, particularly the latter, affected individuals constitute reservoirs of infection.

For HBV infection, the term "healthy carrier" has been used for an individual with HBsAg and anti-HBe, but without HBeAg. These patients have normal aminotransferases, low or undetectable serum HBV DNA, and lack of significant inflammation or liver injury on biopsy.

(Ref: Robbins/10th/837)

Nice to Know:

Hepatitis C virus: Hepatitis C virus (HCV) rarely causes symptomatic acute hepatitis, but it is the **most common cause** of **chronic viral hepatitis.**

In contrast with HBV, **chronic disease** occurs in **80% to 90%** of HCV-infected individuals, and approximately **20%** of these individuals **progress to cirrhosis** over 20 to 30 years.

The **mode of transmission** is **parenteral**. The most common **risk factors** for HCV infection are:

- Intravenous drug abuse
- Multiple sex partners
- Needle-stick injury
- Multiple contacts with an HCV-infected person
- Transfusion-related transmission
- Perinatal transmission can occur in children
- Unknown (One-third of infected individuals have no identifiable risk factors).

(Ref: Robbins/10th/834)

Q. Male of 30 years of old having history of recent blood transfusion presented with jaundice, weakness, anorexia, mild right hypochondriac pain and high of SGPT. Give the provisional diagnosis. What are the possible outcomes of such case? (DU-21Ja,20/19Nv)

Ans.

Provisional diagnosis: Viral hepatitis (HBV infection).

Possible outcome of hepatitis-B virus infection: *Please write from above.*

Alcoholic Liver Disease

Q. Give an outline of the spectrum of liver diseases associated with alcohol abuse. (DU-10Ju)

Q. Short note: Alcoholic liver disease.

Ans.

Alcoholic liver disease: Alcoholic liver disease is a **chronic disorder** that can give rise to **steatosis, alcoholic hepatitis, progressive steato-fibrosis,** and marked **derangement of vascular perfusion** leading eventually to **cirrhosis.**

Excessive alcohol (ethanol) consumption is a major cause of liver disease in most Western countries. Consumption of 80 g/day of alcohol is considered to be the threshold for development of alcoholic liver disease, but may be lower in women.

(Ref: Robbins/10th/842)

Spectrum of liver diseases associated with alcohol abuse: There are *three* distinctive, albeit overlapping, forms of alcoholic liver injury- ***(Important for VIVA)***

(1) Steatosis, or fatty change
(2) Alchoholic steato-hepatitis
(3) Fibrosis, which leads to cirrhosis.

(***N.B***: Only 10% to 15% of alcoholics develop cirrhosis.)

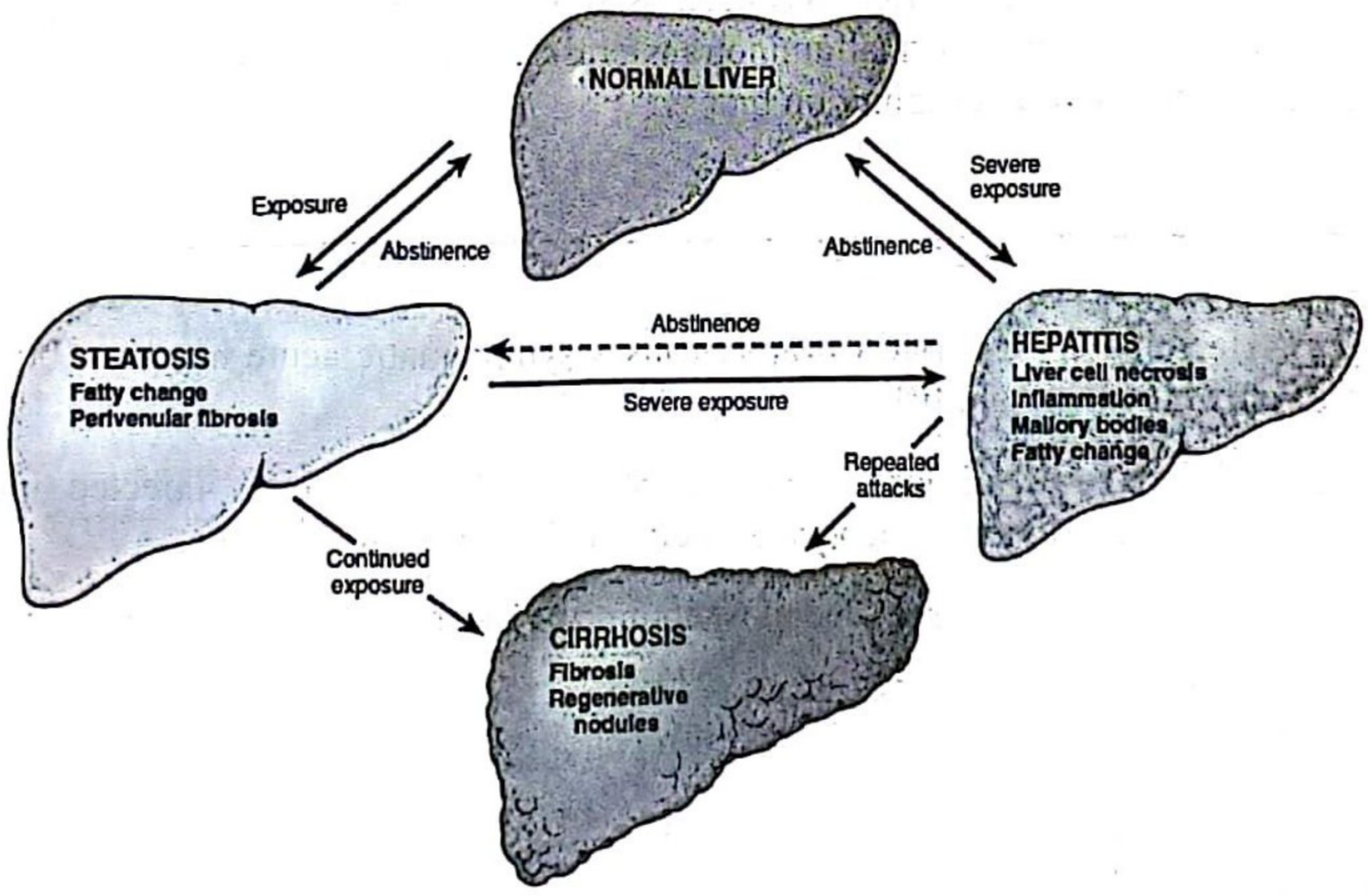


Fig: Alcoholic liver disease. The interrelationships among hepatic steatosis, alcoholic hepatitis, and alcoholic cirrhosis are shown, along with depictions of key morphologic features.

Factors influencing the development of alcoholic liver disease:

1. **Gender:** Women are more susceptible than men, although the majority of patients are men.

2. **Ethnic and genetic differences:** Cirrhosis rates are higher for Africans Americans than for Caucasian Americans, despite similar levels of alcohol consumption. Studies with twins suggest that there is a genetic component in alcohol-induced liver disease (strong family association).
3. **Co-morbid conditions:** Iron overload, non-alcoholic steatohepatitis, and infection with HCV and HBV synergize with alcohol to increase the severity of liver disease.

Laboratory findings: Laboratory findings reflect hepatic dysfunction and include-

- Elevated serum aminotransferases (ratio of serum AST and ALT level 2 : 1 or greater)
- Hyperbilirubinemia
- Variable elevation of serum alkaline phosphatase (ALP)
- Hypoproteinemia (globulins, albumin, and clotting factors)
- Anemia.

Morphology:

Macroscopically:

- The fatty liver of chronic alcoholism is **enlarged** (as heavy as 4 to 6 kg), soft, yellow, and greasy.
- Steatosis may be separated into microvesicular and macrovesicular forms.

Microscopically:

- Ballooned hepatocytes (these are injured, swollen hepatocytes with cleared-out cytoplasm and cytoskeletal damage, which when extensive, results in formation of **Mallory hyaline**).
- Inflammation and necrosis.
- Perivenular / pericellular fibrosis.

In advanced disease, common proximate causes of death:

1. Hepatic coma
2. Massive gastrointestinal hemorrhage
3. Inter-current infection (to which these patients are predisposed)
4. Hepatorenal syndrome (often following a bout of alcoholic hepatitis)
5. Hepatocellular carcinoma (in 1 to 6% of cases annually).

(Ref: Robbins/10th/842-845)

Nice to Know:

Nonalcoholic Fatty Liver Disease (NAFLD): NAFLD is defined as the presence of hepatic steatosis (fatty liver) in individuals who do not consume alcohol or do so in small quantities and who do not have another cause of secondary hepatic fat accumulation (e.g. HCV, Wilson disease, medications).

NAFLD is associated with obesity, diabetes mellitus type 2, and hyperlipidemia, all components of the metabolic syndrome.

Complicatios of NAFLD:

- Decompensated cirrhosis
- Hepatocellular carcinoma.

(***N.B*:** The term ***nonalcoholic steatohepatitis*** (or its common acronym ***NASH***) is reserved for NAFLD patients who demonstrate steatohepatitic injury with histologic features similar to those seen with alcoholic hepatitis.)

(Ref: Robbins/10th/846)

Haemochromatosis

Q. Short note: Haemochromatosis. ***(Important for VIVA)***

Ans.

Haemochromatosis: Hemochromatosis is caused by **excessive iron absorption**, most of which is deposited in the liver and pancreas, followed by the heart, joints, and endocrine organs.

When hemochromatosis results from an **inherited disorder**, it is referred to as ***hereditary hemochromatosis***. When accumulation occurs as a **consequence of parenteral administration of iron**, usually in the form of transfusions, or other causes, it is called ***secondary hemochromatosis***.

Important involved organs: Liver, pancreas, heart, joints, and endocrine organs.

Types & causes:

1. **Primary / hereditary haemochromatosis**
2. **Secondary haemochromatosis (Hemosiderosis)**
   - **a. Parenteral iron overload due to red cell transfusions**
     - Severe chronic hemolytic anemias (e.g. sickle cell disease)
     - Severe forms of thalassemia
     - Bone marrow failure (e.g. aplastic anemia)
   - **b. Conditions associated with increased iron uptake**
     - β-Thalassemia
     - Myelodysplastic syndrome
   - **c. Increased oral intake of iron**
     - African iron overload (Bantu siderosis)
   - **d. Congenital atransferrinemia**
   - **e. Chronic liver disease**
     - Alcoholic liver disease
     - Porphyria cutanea tarda
   - **f. Neonatal hemochromatosis.**

(Ref: Robbins/10th/848)

Wilson Disease

Free copper is normally taken up by **hepatocytes** and incorporated into **apoceruloplasmin** to form ***ceruloplasmin,*** which is secreted into the **blood**. Ceruloplasmin accounts for 90% to 95% of plasma copper. **Excess copper** within hepatocytes that is not incorporated into ceruloplasmin is **sequestered in lysosomes** and transported into the **bile**, from which it is eventually excreted in the **feces**.

(Ref: Robbins/10th/850)

Q. Short note: Wilson disease. ***(Important for VIVA)***

Ans.

Wilson disease (hepato-lenticular degeneration): It is an **autosomal recessive disorder** caused by mutation of the **ATP7B gene**, resulting in **impaired copper excretion** into bile and a failure to incorporate copper into ceruloplasmin. This disorder is marked by the **accumulation of toxic levels of copper** in many tissues and organs, principally in the **liver**, **brain**, and **eye**.

Pathogenesis: In this disease, the initial steps of Cu absorption and transport to liver are normal. **Deficiency of ATP7B decreases copper transport into bile, impairs its incorporation into ceruloplasmin**, and **inhibits ceruloplasmin secretion into the blood**. These defects lead to a **decrease in circulating ceruloplasmin** accompanied by the **accumulation of copper in hepatocytes**.

Thus, excess hepatic copper causes toxic injury by following three mechanisms:

(1) Promoting the formation of free radicals by the Fenton reaction
(2) Binding to sulfhydryl groups of cellular proteins
(3) Displacing other metals from hepatic metalloenzymes.

Hepatocyte injury causes non-ceruloplasmin-bound copper to be spilled into the blood and accumulate in certain tissues, particularly the **basal ganglia of the brain** and the **cornea**. Concomitantly, **urinary excretion of copper markedly increases**, but not to levels sufficient to prevent deposition of copper in tissues.

Clinical features:

- Age at onset ranges from **6 to 40 years of age** (average age is 11.4 years).
- Neurologic involvement may lead to **movement disorders** (tremor, poor coordination, chorea or choreoathetosis) or **rigid dystonia** (spastic dystonia, masklike facies, rigidity, and gait disturbances).
- Eye lesions called K-F rings (**Kayser-Fleischer rings**)
- **Psychiatric symptoms**
- **Hemolytic anemia** (due to red cell membrane damage caused by oxidants produced by free copper).

Diagnostic tests:

- Decreased serum ceruloplasmin
- Increased hepatic copper content (the most sensitive and accurate test)
- Increased urinary excretion of copper (the most specific test)
- Sequencing of the *ATP7B* gene
- Demonstration of Kayser-Fleischer rings by slit examination.

Treatment:

- Early recognition and long-term copper chelation therapy (with D-penicillamine or trientine) or zinc-based therapy (which blocks uptake of dietary copper in the gut) is effective.
- Individuals with hepatitis or unmanageable cirrhosis require liver transplantation, which can be curative.

(Ref: Robbins/10th/850-851)

Q. What is K-F ring? ***(Important for VIVA)***

Ans.

K-F ring (Kayser-Fleischer ring): Toxic brain injury primarily involves the **basal ganglia**, and nearly all patients with neurologic involvement develop **eye lesions** called **K-F rings (Kayser-Fleischer rings)**, green to brown deposits of copper in Descemet membrane in the limbus of the cornea.

(Ref: Robbins/10th/850)

Fig: Kayser-Fleischer ring.

Primary Biliary Cirrhosis (PBC)

Q. What is primary biliary cirrhosis? ***(Important for VIVA)***

Ans.

Primary biliary cirrhosis (PBC): PBC is an autoimmune disease characterized by inflammatory destruction of small- and medium-sized intrahepatic bile ducts.

(Ref: Robbins/10th/857)

Hepatocellular Carcinoma

Q. Write down the etiology of hepatocellular carcinoma. (DU-07Ja)
Q. Give the morphology of hepatocellular carcinoma.
Q. Short note: Hepatocellular carcinoma.

Ans.

Hepatocellular carcinoma: Most **primary liver cancers** arise from hepatocytes and are termed **hepatocellular carcinoma (HCC)** (also known erroneously as **hepatoma**).

Incidence: It accounts for approximately 5.4% of all cancers worldwide and is one of the most common cancers in geographic regions with high rates of hepatitis B infection. There is a pronounced male predominance, as high as 8 : 1.

Causes: Most HCCs occur in the setting of ***chronic liver disease*** with ***cirrhosis***, while 15% to 20% arise in ***noncirrhotic livers***. The most common underlying diseases are-

- Chronic viral hepatitis (B and C)
- Hereditary hemochromatosis
- α_1-antitrypsin deficiency
- Alcoholic liver disease
- Non-alcoholic fatty liver disease
- Aflatoxin (a mycotoxin produced by *Aspergillus* species)
- Wilson disease
- Chronic biliary diseases

Clinical features: The clinical manifestations of HCC are nonspecific and include-

- Abdominal pain
- Malaise
- Fatigue
- Weight loss
- Hepatomegaly
- Features of underlying chronic liver disease.

Investigations:

- Elevated levels of serum α-fetoprotein
- Ultrasonography of whole abdomen
- CT scan and MRI with contrast studies
- Triphasic CT scan (early enhancement of the tumor due to contrast uptake in the arterial phase, followed by rapid venous washout, is considered *diagnostic* of HCC).

Morphology:

***Gross*:**

- HCC may form a **single mass** or **multiple discrete masses**, or it may **diffusely infiltrate** the liver.
- They may be **pale** and **yellow** due to fatty change or **green** due to cholestasis.

***Microscopic*:**

- HCC ranges from **well-differentiated** to **highly anaplastic undifferentiated** lesions.
- **Well and moderately differentiated** HCC are composed of cells that resemble normal hepatocytes, while **poorly differentiated** tumors show marked cytologic atypia.
- The **tumor cells** grow in **thick plates** or **trabeculae, pseudoglandular structures** with **bile plugs,** or **sheets**.

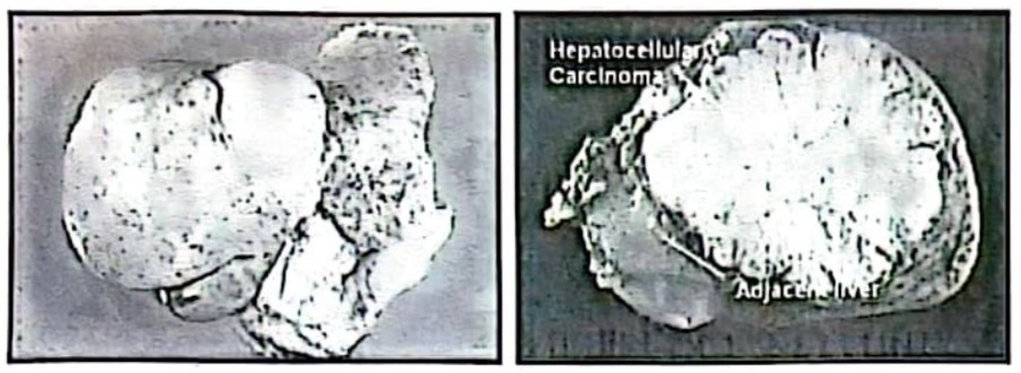


Fig: Hepatocellular carcinoma.

Metastasis:

- Tumors larger than 2 cm are more likely to be associated with vascular invasion and intrahepatic metastases.
- Hematogenous metastases, especially to the lung, tend to occur late in the disease.
- Lymph node metastases occur in <5% of cases.

Prognosis: The overall 5-year survival rate is 30% for tumor confined to the liver and only 5% to 10% for cases with extrahepatic spread.

Cause of death in HCC:

- Cachexia
- Gastro-intestinal or esophageal variceal bleeding
- Liver failure with hepatic coma
- Rupture of the tumour with fatal haemorrhage (rarely).

(Ref: Robbins/10th/868)

Q. A male of 55 years complaining of weakness, hepatomegaly for few months. He has history of hepatitis B virus infection few years back. USG shows a SOL in liver. What is the probable diagnosis? How will you proceed to diagnose the case? (DU-23M)

Q. A 45 years male has been suffering from weakness and tiredness for last 2 months. On examination hepatomegaly is found. He has past history of hepatitis B virus infection. USG shows SOL in the left lobe of liver. (BUP-18Nv)

a) **What is the probable diagnosis?**
b) **How will you proceed to diagnose the case?**

Q. A male of 55 years complaints of weakness, tiredness and hepatomegaly for the last few months. He has past history of hepatitis B virus infection few years back. USG shows SOL the left lobe of liver. (BUP-16Ju)

a) **What is the probable diagnosis?**
b) **How will you proceed to diagnose the case?**

Q. A male of 59 years has presented with weakness, tiredness, and hepatomegaly for few months. He has got history of hepatitis B infection few years back. UCG reveals a SOL in the right lobe of the liver. How will you proceed to diagnose the patient and what are your expected findings? (DU-08Ju)

Ans.

History: History of hepatitis B infection few years back.

Clinical examination: Hepatomegaly.

Investigation: UCG reveals a SOL (space occupying lesion) in the right lobe of the liver.

Probable diagnosis: Hepatocellular carcinoma (HCC).

To diagnose, I shall do the following investigations:

1) **Liver function test**
   - Serum total protein - reduced
   - Serum albumin - reduced
   - A/G ratio - reduced / altered
   - Prothrombin time (PT) - prolonged
   - Serum bilirubin - may be increased
2) Serum α-fetoprotein (elevated in 50% cases of HCC)
3) Serum CEA level (may be elevated)
4) Imaging studies including-
   - Ultra-sonography of whole abdomen (SOL in the liver)
   - Computed tomography (CT scan)
   - Magnetic resonance imaging (MRI)
   - Triphasic CT scan (early enhancement of the tumor due to contrast uptake in the arterial phase, followed by rapid venous washout, is considered *diagnostic* of HCC)
5) Image guided core needle biopsy / FNAC for liver SOL followed by histopathology.

Liver Abscess

Q. Short note: Liver abscess. (RU-08Ju)

Ans.

Liver abscess: It is a form of **liver infection** that is common in **developing countries**.

Cause: Liver abscesses are usually caused by **echinococcal** and **amebic infections**, and less commonly, by other **protozoal** and **helminthic organisms**. Most abscesses are pyogenic, representing a complication of bacterial infection elsewhere.

Portal of entry: The organisms reach the liver by-

- Portal vein
- Arterial supply
- Ascending infection in the biliary tract (ascending cholangitis)
- Direct invasion of the liver from a nearby source, or
- A penetrating injuty.

The majority of hepatic abscesses used to result from portal spread of intra-abdominal infections (e.g. appendicitis, diverticulitis, colitis). With improved management of these conditions, spread now occurs primarily through the biliary tree or the arterial supply in patients suffering from some form of immune deficiency (e.g. old age with debilitating disease, immune-suppression or cancer chemotherapy with marrow failure). In these settings abscesses may develop without a primary focus elsewhere.

Morphology:

- It may occur as solitary or multiple lesions, ranging in size from mm to massive lesions many cm in diameter
- Bacteremic spread tends to produce multiple small abscesses, whereas direct extension and trauma usually cause solitary large abscesses
- Biliary abscesses, which are usually multiple, may contain purulent material from adjacent bile ducts
- The causative organism can occasionally be identified in the case of fungal or parasitic abscesses
- Rupture of subcapsular liver abscesses has also led to peritonitis or localized peritoneal abscesses
- Echinococcal infection has a characteristic cystic structure; the wall is laminated and hooklets and intact organisms can be identified
- Calcification in the cystic wall is common.

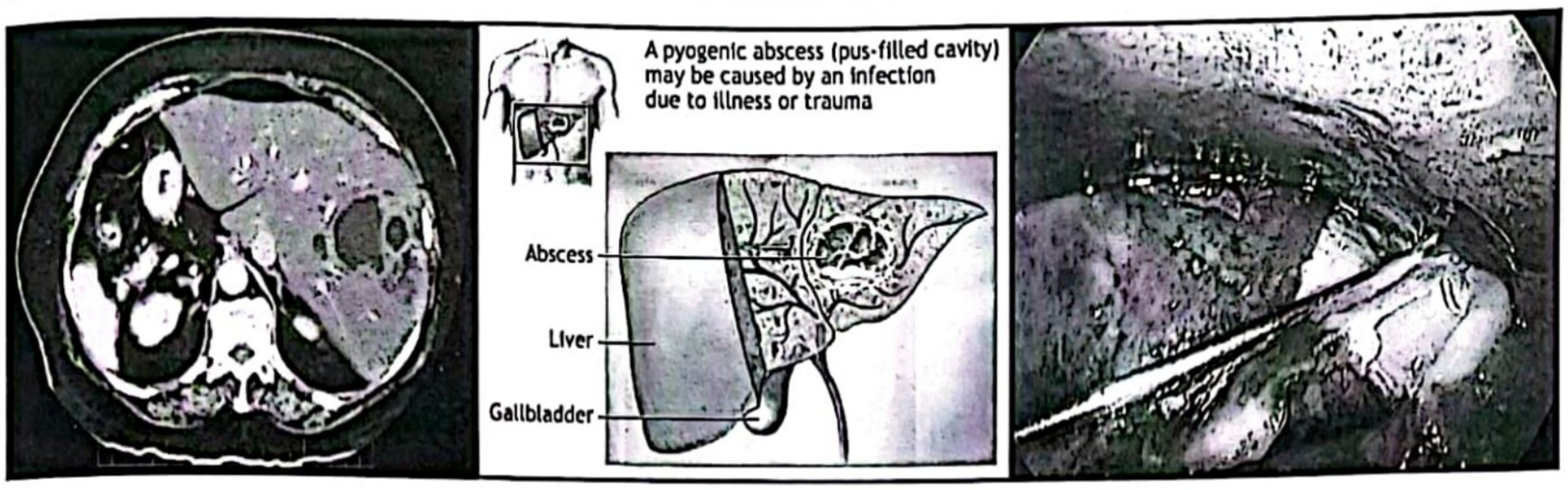


Fig: Liver abscess.

Clinical features:

a. Fever
b. Right upper quadrant pain
c. Tender hepatomegaly
d. Jaundice.

Management:

a. Antibiotic therapy (for the smaller lesions)
b. Surgical drainage (for the larger lesions).

Prognosis: Mortality rate with large liver abscesses ranges from 30% to 90%. With early recognition and management, up to 80% of patients can survive.

(Ref: Robbins/10th/839 + 8th/854)

Gall Bladder & Biliary Tract

Q. Name the pathological conditions of gall bladder and extra-hepatic biliary ducts.

Ans.

Diseases of gall bladder and extra-hepatic biliary ducts:

***Diseases of gall bladder*:**

1. **Congenital anomalies:**
   - Agenesis (absence of GB)
   - Double gall Bladder
   - Bilobed Gall Bladder
   - Aberrant locations of the GB
   - Folded fundus (Phrygian cap)
2. **Cholecystitis:**
   - Acute cholecystitis
   - Chronic cholecystitis
3. **Cholelithiasis (gall stones):**
   - Cholesterol stone (90%)
   - Pigment stone (10%)
4. **Tumors of gall bladder:**
   - **Benign:** Carcinoids, fibromas, myomas, neuromas, haemangiomas, adenomas, polyp.
   - **Malignant:** Carcinoma of gall bladder (adenocarcinoma), carcinoid tumour.

***Diseases of extra-hepatic biliary ducts*:**

1. Biliary atresia
2. Choledocholithiasis and ascending cholangitis
3. Choledocal cysts

4. Fibropolycystic disease
5. Tumour: Cholangiocarcinoma.

(Ref: Robbins/10th/823,872-877)

Fig: Phrygian cap of the gallbladder; the fundus is folded inward.

Q. Define gall stones. Give the mechanism of gall stone formation. (RU-17Nv,11Ju,09/06/05Ja)
Q. Write in brief pathogenesis of gall stone formation. (RU-19/18Nv,13Ja)
Q. Write down the pathogenesis of cholesterol gall stone formation. (RMU-22M,19/18Nv,13Ja)
Q. Short note: Pathogenesis of gall stone. (RU-14Ju)
Q. Short note: Gall stone. (CU-20Nv)

Ans.

Gall stones: Gall stones are concretions produced in the gall bladder due to abnormal composition of bile. Super-saturation of bile with cholesterol or bilirubin salts promotes stone formation.

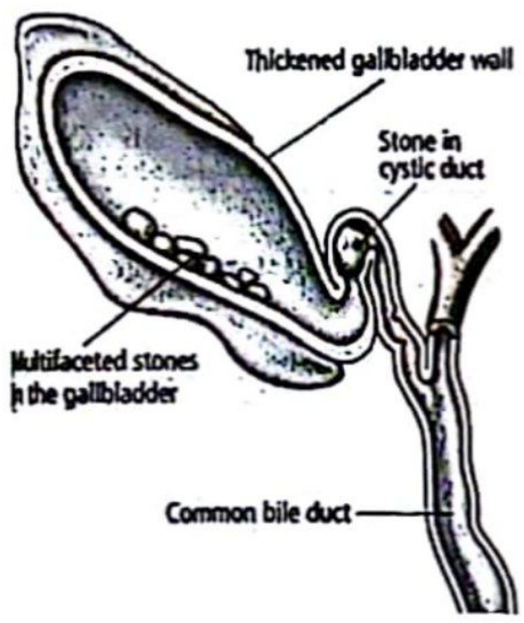


Fig: Gall stone and cholecystitis.

Pathogenesis of gall stone formation: ***(Important for VIVA)***

A) ***Pathogenesis of cholesterol stones*:**

Cholesterol concentrations exceed the solubilizing capacity of bile (supersaturation), due to hepatocellular hypersecretion of cholesterol & gall bladder hypomotility

↓

Cholesterol can no longer remain dispersed and nucleates into solid cholesterol monohydrate crystals

↓

Hypersecretion of mucus in the gall bladder traps the nucleated crystals

↓

Aggregation of nucleated crystals

↓

Stone formation

B) ***Pathogenesis of pigment stones*:** Pigment gall stones are complex mixtures of abnormal insoluble calcium salts of unconjugated bilirubin along with inorganic calcium salts.

i) Infection of the biliary tract with *E. coli, Ascaris lumbricoides,* or by liver flukes (*C. sinensis*)
↓
Inhibits bilirubin glucuronide conjugation by release of microbial β-glucuronidase
↓
↑Unconjugated bilirubin
↓
Mixed with abnormal insoluble calcium salts
↓
Formation of pigment stone

ii) Chronic haemolysis due to any cause → ↑Excretion of conjugated bilirubin & promote formation of unconjugated bilirubin → Formation of pigment stone.

(Ref: Robbins/10th/873)

Q. Mention the etiology, classification (RMU-22/21/20/18Nv,17/13/06Ja) **& complication** (RMU-23M,22/21/20Nv,18Nv/Ja,17Nv/Ja,16/15/13/08/06Ja) **of gall stone.**
Q. What are the factors that favor stone formation within gallbladder? (DU-09Ja)
Ans.

Classification of gall stone: ***(Important for VIVA)***

1. **Cholesterol stone:** About 90% are cholesterol stones, containing more than 50% of **crystalline cholesterol monohydrate.**
2. **Pigment stones:** Composed predominantly of **bilirubin calcium salts.**

(Ref: Robbins/9th/876)

Etiology / risk factors for gall stone: ***(Important for VIVA)***

1. **Cholesterol stones:**
   - Demography: Northern Europe, North and South America, Native Americans, Mexican Americans
   - Advancing age
   - Female sex hormones
     - Female gender
     - Oral contraceptives
     - Pregnancy
   - Obesity and metabolic syndrome
   - Rapid weight reduction
   - Gallbladder stasis
   - Inborn disorders of bile acid metabolism
   - Hyperlipidemia syndromes
2. **Pigment stones:**
   - Demography: Asians more than Westerners, rural more than urban
   - Chronic haemolytic syndromes
   - Biliary infection: *Salmonella typhi*, *Ascaris lumbricoides*, *Escherichia coli*, *C. sinensis*
   - Gastrointestinal disorders: Ileal disease (e.g. Crohn disease), ileal resection or bypass, cystic fibrosis with pancreatic insufficiency.

(Ref: Robbins/10th/873)

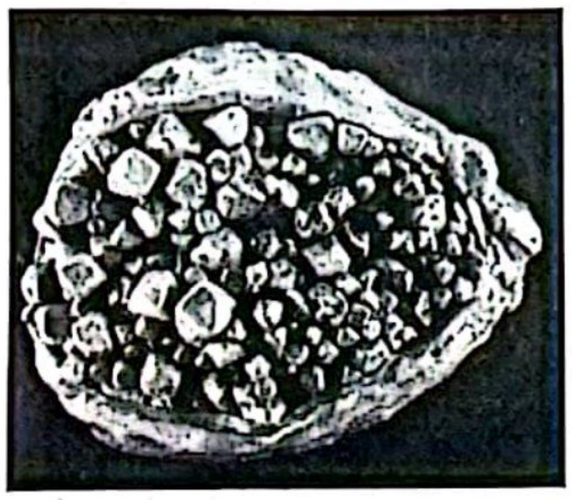


Fig: Cholesterol gallstones.

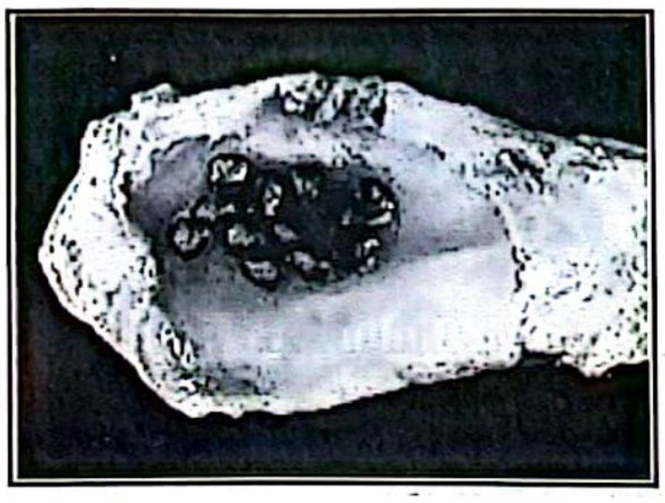


Fig: Pigment gall stones.

Complications of gall stone:

a. Acute cholecystitis
b. Chronic cholecystitis
c. Empyema of gall bladder
d. Perforation
e. Fistulae *(between gall bladder and duodenum or colon)*
f. Inflammation of the biliary tree (cholangitis)
g. Obstructive cholestasis or pancreatitis
h. Intestinal obstruction ("gallstone ileus")
i. Carcinoma of the gall bladder.

(Ref: Robbins/10th/875)

Q. Short note: Acute cholecystitis.

Ans.

Acute cholecystitis: It is an ***acute inflammation of the gall bladder***, precipitated in 90% of cases by obstruction of the neck of the gall bladder or the cystic duct by a gallstone.

Risk factors for acute cholecystitis:

1. **Acute calculous cholecystitis** (90% cases)
   - Gall stones
2. **Acute acalculous cholecystitis** (10% cases)
   - Sepsis with hypotension and multisystem organ failure
   - Immunosuppression
   - Major trauma and burns
   - Diabetes mellitus
   - Infections.

Clinical features:

1. Progressive right upper quadrant or epigastric pain (colicky / dull and constant) that lasts for more than 6 hours.
2. Fever, anorexia, tachycardia, sweating, nausea, and vomiting.

Laboratory tests:

1. **CBC:** Leukocytosis.
2. **Serum bilirubin level:** Raised (suggests obstruction of the common bile duct)
3. **Serum alkaline phosphatase (ALP) level:** Raised.

(***N.B***: A definitive diagnosis can only be made following **USG / CT scan of whole abdomen** with special attention to hepatobiliary system.)

(Ref: Robbins/10th/875; BRS Pathology/5th/255)

Q. A female of 22 years presented with a colicky pain in the right hypochondriac region along with fever and vomiting. (CU-20Nv)

a) **What is your possible diagnosis?**
b) **What are the possible causes of it?**
c) **What are the laboratory tests and positive findings to establish the diagnosis?**

Ans.

Possible diagnosis: Acute cholecystitis.

Possible causes: *Please write from above.*

Laboratory tests and positive findings to establish the diagnosis: *Please write from above.*

Q. What is chronic cholecystitis?

Q. What are the morphological changes in chronic cholecystitis? (CMU-22M, RU-19Nv)

Ans.

Chronic cholecystitis: Chronic inflammation of the gallbladder due to chemical irritation from longstanding cholelithiasis, with or without superimposed bouts of acute cholecystitis.

Morphological changes in chronic cholecystitis: The morphologic changes in chronic cholecystitis are extremely variable and sometimes minimal.

Gross:

- Gallbladder may be **contracted**, of **normal size**, or **enlarged.**
- **Thickening** of the **wall** as a result of **extensive fibrosis**
- **Serosa** is usually **smooth** and **glistening.**
- **Subserosa** and **submucosa** are often **thickened from fibrosis** (mucosa itself is generally preserved)
- Occassionally the **lumen** contains **green-yellow, mucoid bile** and usually **stones.**
- **On sectioning,** the **wall is variably thickened,** and has an **opaque gray-white appearance.**

Microscopic:

- Degree of inflammation is variable.
- Gallbladder **mucosa** and **subserosal fibrous tissue** may be infiltrated by **chronic inflammatory cells** (e.g. lymphocytes, plasma cells, macrophage etc.).
- **Rokitansky-Aschoff sinuses** (pseudodiverticula or pockets in the wall of the gallbladder / entrapped epithelial crypts) may be found, which is characterized by **outpouchings / herniation of gallbladder mucosa into the muscular wall.**
- Extensive **dystrophic calcification** within the wall may yield a **porcelain gallbladder,** which is characterized by **shrunken, hard gallbladder** due to **chronic inflammation & fibrosis.**
- An atrophic, chronically obstructed, dilated gallbladder containing clear secretions (a condition known as **hydrops of the gallbladder**) & xanthoma cells (lipid containing cells with foamy cytoplasm) may be found in **xanthogranulomatous cholecystitis.**

(Ref: Robbins/10th/876; BRS Pathology/5th/255)

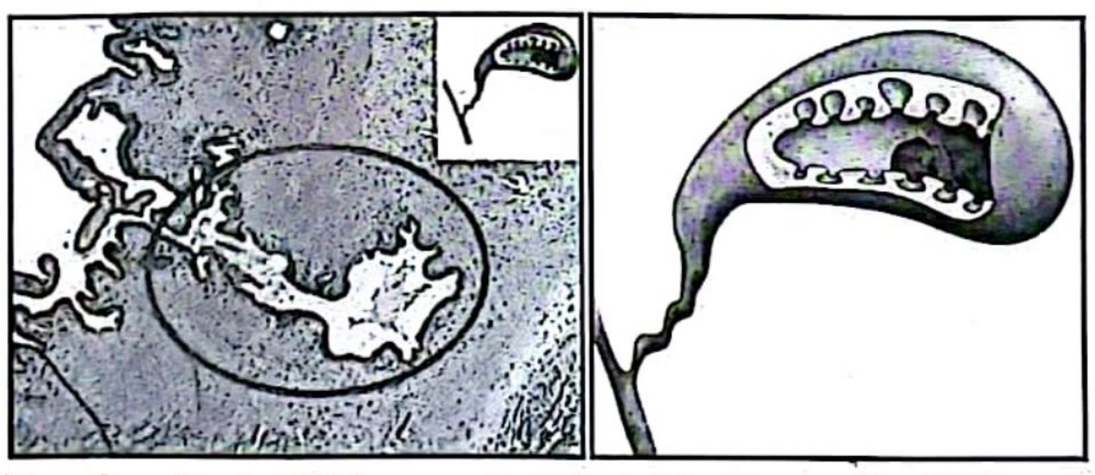


Fig: Rokitansky-Aschoff sinuses (pockets) in the wall of the gall bladder.

Q. What are the potential complications of chronic cholecystitis?

Ans.

Potential complications of chronic cholecystitis:

- Bacterial superinfection with cholangitis or sepsis.
- Gallbladder perforation and local abscess formation.
- Gallbladder rupture with diffuse peritonitis.
- Biliary enteric (cholecystenteric) fistula, with drainage of bile into adjacent organs, entry of air and bacteria into the biliary tree, and potentially, gallstone-induced intestinal obstruction (ileus).
- Aggravation of preexisting medical illness, with cardiac, pulmonary, renal, or liver decompensation.

(Ref: Robbins/10th/876)

Q. What type of carcinoma occurs in gall bladder?

Ans.

Carcinoma of the gall bladder:

- Most carcinomas of the gall bladder are **adenocarcinomas** (as lined by columnar epithelium).
- About 5% are **squamous cell carcinoma** or have **adenosquamous** differentiation.
- Squamous cell carcinoma of the gall bladder may occur in long-standing gall stone, as gall stone causes squamous metaplasia of gall bladder epithelium.
- A minority may show **carcinoid** or a variety of mesenchymal features (**carcinosarcoma**).

(Ref: Robbins/10th/876 + 9th/880)

Q. Mention the morphology of carcinoma of gall bladder.

Ans.

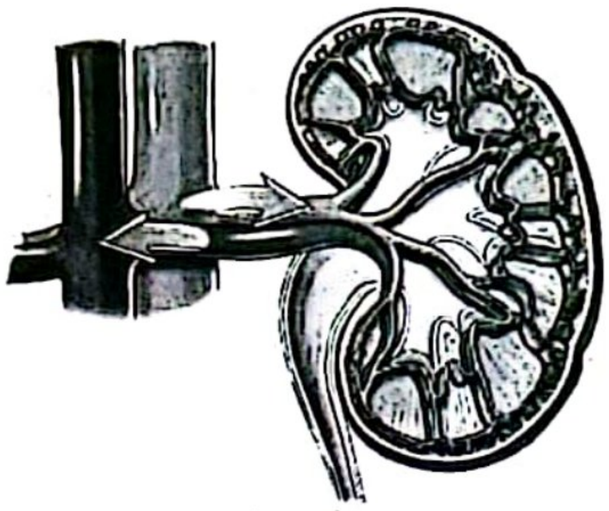
Morphology of carcinoma of gall bladder: Carcinomas of the gall bladder show two patterns of growth- **infiltrating** and **exophytic.**

- **Infiltrating pattern:** It is more common and appears diffuse thickening and induration of the gallbladder wall. Deep ulceration can cause direct penetration of the gall bladder wall or fistula formation to adjacent viscera into which the neoplasm has grown.
- **Exophytic pattern:** It grows into the lumen as an irregular, cauliflower mass. The luminal portion may be necrotic, hemorrhagic, and ulcerated. The most common sites of involvement are the fundus and the neck; about 20% involves the lateral walls.

(Ref: Robbins/10th/877 + 9th/880)

CHAPTER 08

RENAL SYSTEM



HISTOLOGY: The parenchyma of each kidney is composed of approximately one million microstructures called **nephrons**. A nephron, in turn, consists of 5 major parts, each having a functional role in the formation of urine: the glomerular capsule (glomerulus and Bowman's capsule), the proximal convoluted tubule (PCT), the loop of Henle, the distal convoluted tubule (DCT), and the collecting ducts.

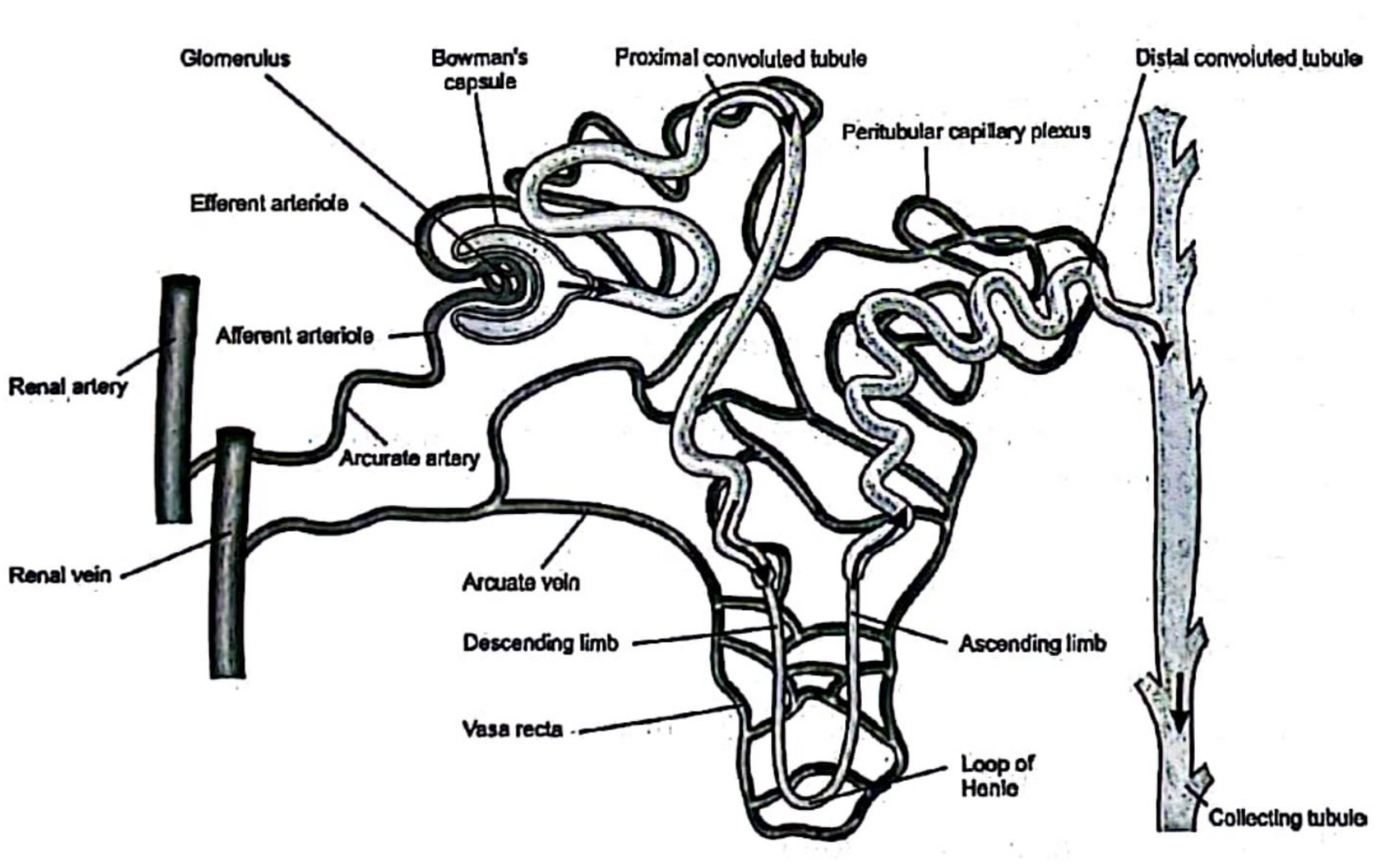


Fig: Structure of a nephron.

The major *function* of glomerulus is complex filtration from the capillaries to the urinary space. The **barrier to glomerular filtration** consists of the following 3 components:

i. **Fenestrated endothelial cells** lining the capillary loops.
ii. **Glomerular basement membrane (GBM)** on which the endothelial cells rest.
iii. **Filtration slit pores** between the foot processes of the visceral epithelial cells (podocytes) external to GBM.

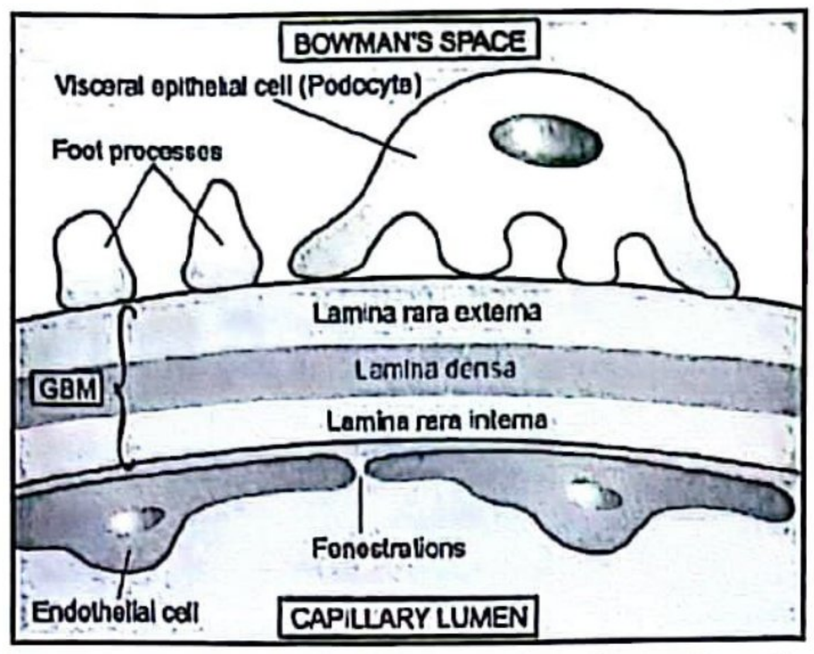


Fig: Ultrastructure of glomerular filtration barrier.

Diseases of the Kidney

Q. Name the diseases of kidney.

Ans.

Diseases of kidney:

1. **Congenital and developmental anomalies:**
   - Agenesis of the kidney
   - Hypoplasia
   - Ectopic kidney
   - Horseshoe kidney
   - Polycystic kidney
2. **Glomerular diseases:**
   - Nephritic syndrome
   - Nephrotic syndrome
   - Hereditary e.g. Fabry disease, Alport syndrome
   - Systemic e.g. lupus nephritis, Henoch-Schönlein purpura, diabetic nephropathy, amyloidosis
3. **Tubular and interstitial diseases:**
   - Acute tubular injury / necrosis
   - Tubulointerstitial nephritis
   - Pyelonephritis and urinary tract infection (UTI)
   - Drug induced nephropathy
   - Others: Urate nephropathy, hypercalcemia and nephrocalcinosis, light-chain cast nephropathy ("myeloma kidney")
4. **Vascular diseases:**
   - Nephrosclerosis
   - Renal artery stenosis
   - Thrombotic microangiopathies e.g. thrombotic thrombocytopenic purpura (TTP)
   - Others: Atherosclerotic ischemic renal disease, atheroembolic renal disease, sickle cell nephropathy, renal infarcts
5. **Cystic diseases of the kidney** (see below)
5. **Urinary tract obstruction** (obstructive uropathy)
6. **Urolithiasis** (renal calculi, stones)
7. **Tumours:**
   a. ***Benign*:**
      - Renal papillary adenoma
      - Angiomyolipoma

- Oncocytoma
- Mesoblastic nephroma

b. ***Malignant*:**

- **Primary:**
  - Renal cell carcinoma (adenocarcinoma of the kidney)
  - Urothelial carcinomas of the renal pelvis
  - Wilms tumour (nephroblastoma)
- **Secondary:** Blood-borne metastases chiefly from cancers of the lungs, breast and stomach.

(Ref: Robbins/10th/895-952; Harsh Mohan/7th/680)

Q. What are the cystic diseases of the kidney?

Ans.

Cystic diseases of the kidney:

1. Simple renal cyst
2. Acquired cystic disease
3. Polycystic kidney disease
   - Autosomal-dominant (adult) polycystic kidney disease (ADPKD)
   - Autosomal-recessive (childhood) polycystic kidney disease (ARPKD)
4. Cystic diseases of the renal medulla
   - Medullary sponge kidney
   - Nephronophthisis
4. Multicystic renal dysplasia.

(Ref: Robbins/10th/895,941; Harsh Mohan/7th/644)

Q. What are the clinical manifestations of renal diseases? (RU-18Nv)

Ans.

Clinical manifestations of renal diseases: (For VIVA)

1. **Azotemia** (elevation of BUN and creatinine levels)
2. **Uremia** (clinical signs and symptoms of azotemia with biochemical abnormalities)
3. **Nephritic syndrome**
4. **Nephrotic syndrome**
5. **Asymptomatic hematuria or proteinuria**
6. **Acute kidney injury** (previously called acute renal failure)
7. **Chronic kidney disease** ((previously called chronic renal failure)
8. **End-stage renal disease** (GFR is less than 5% of normal)
9. **Renal tubular defects** (dominated by polyuria, nocturia, and electrolyte disorders e.g. metabolic acidosis)
10. **Urinary tract obstruction/infection** {characterized by bacteriuria and pyuria (bacteria and leukocytes in the urine)}. It may affect the kidney (pyelonephritis) or the bladder (cystitis).
11. **Nephrolithiasis** (renal stones) manifested by spasms of severe pain (renal colic) and hematuria.

(Ref: Robbins/10th/896)

Q. Enumerate the glomerular diseases. (RMU-21M,17Nv,15Ju,11Ja)

Q. Classify glomerular diseases. (CMU-23/22M, RMU-22/19Nv,18Nv/Ja,17Ja,14Ju,13Ja, SU-20Nv,14Ju)

Q. What are the primary glomerular diseases? (DU-23M,19Nv,11Ju, SU-19Nv,17M,16Ja,10Ju, CU-13Ja)

Q. Name primary glomerulopathies. (SU-03S)

Ans.

Glomerular diseases:

A) **Primary glomerular diseases** (glomeruli are the predominant site of involvement)**:**
1. Minimal-change disease (lipoid nephrosis)
2. Membranous glomerulonephritis
3. Membranoproliferative glomerulonephritis
4. Focal segmental glomerulosclerosis
5. IgA nephropathy (Berger's disease)
6. Chronic glomerulonephritis
7. Acute glomerulonephritis
8. Rapidly progressive (crescentic) glomerulonephritis

{মনে রাখার উপায়ঃ **3M Formula-1 (I) CAR**}

B) **Secondary glomerular diseases** (systemic diseases secondarily affect the glomeruli)**:**
1. Systemic lupus erythematosus (lupus nephritis)
2. Diabetic nephropathy
3. Amyloidosis
4. Goodpasture syndrome
5. Polyarteritis nodosa
6. Wegener granulomatosis (granulomatosis with polyangiitis)
7. Microscopic polyangiitis
8. Henoch-Schönlein purpura
9. Cryoglobulinaemia
10. Systemic infectious diseases (*bacterial* e.g. bacterial endocarditis, syphilis, leprosy; *viral* e.g. HBV, HCV, HIV; *parasitic* e.g. falciparum malaria, filariasis etc.)

C) **Hereditary disorders:**
1. Alport syndrome
2. Thin basement membrane disease
3. Fabry disease.

(Ref: Robbins/10th/898; Harsh Mohan/7th/647)

*(**N.B:** The **clinical presentation of glomerular disease** is quite variable but in general four features—**proteinuria**, **haematuria**, **hypertension** and **disturbed excretory function** in varying combinations depending upon the underlying condition.)*

(Ref: Harsh Mohan/7th/647)

Q. Name the glomerular syndrome with their manifestations. *(Important for VIVA)*

Ans.

Glomerular syndrome with their manifestations:

Syndrome	Manifestations
1. Nephritic syndrome	Hematuria, azotemia, variable proteinuria, oliguria, edema, and hypertension
2. Nephrotic syndrome	>3.5 gm/day proteinuria, hypoalbuminemia, generalized edema, hyperlipidemia, and lipiduria
3. Rapidly progressive glomerulonephritis	Acute nephritis, proteinuria, and acute renal failure
4. Chronic renal failure	Azotemia → uremia progressing for months to years
5. Isolated urinary abnormalities	Glomerular hematuria and/or subnephrotic proteinuria

(Ref: Robbins/10th/898; Harsh Mohan/7th/647)

{**N.B:** The term ***'azotaemia'*** is used for **biochemical abnormality** characterised by elevation of the blood urea nitrogen (BUN) and creatinine levels, while ***'uraemia'*** is defined as association of these **biochemical abnormalities** with **clinical signs and symptoms**.}

(Ref: Robbins/10th/896; Harsh Mohan/7th/641)

Nice to Know:

- ***Diffuse*:** involving all of the glomeruli in the kidney;
- ***Global*:** involving the entirety of individual glomeruli;
- ***Focal*:** involving only a fraction of the glomeruli in the kidney;
- ***Segmental*:** affecting a part of each glomerulus; and
- ***Capillary loop* or *mesangial*:** affecting predominantly capillary or mesangial regions.

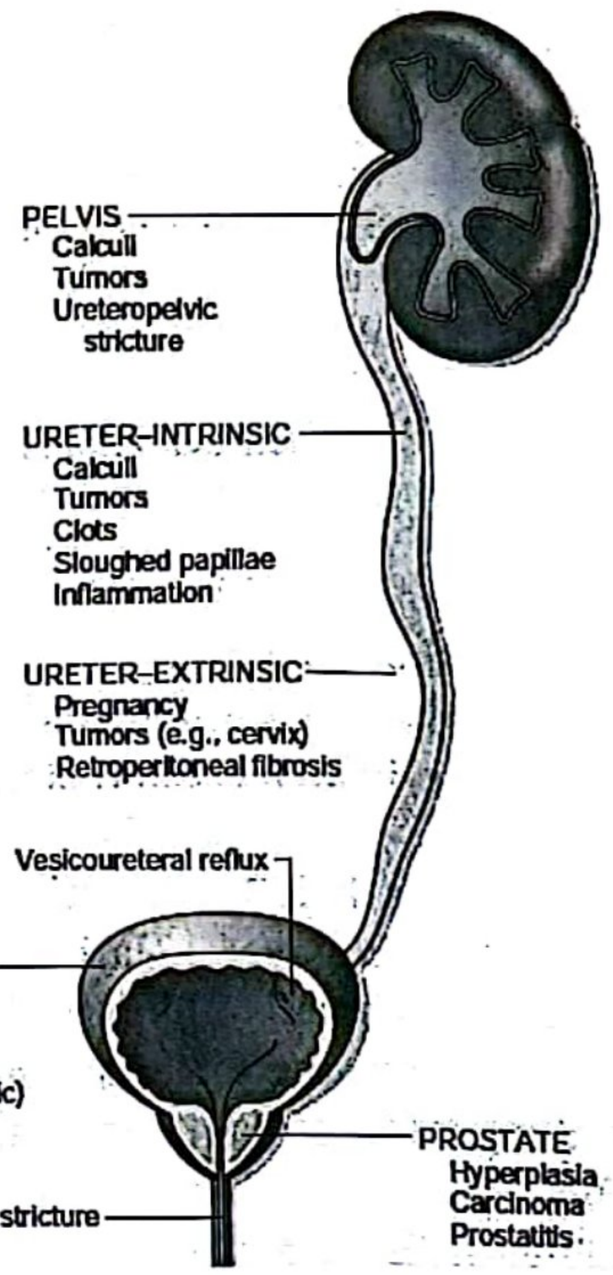
(Ref: Robbins/10th/901)

Q. What are the common causes of urinary tract obstruction?

Ans.

Common causes of urinary tract obstruction (obstructive uropathy):

1. **Congenital anomalies**
   - Posterior urethral valves
   - Urethral strictures
   - Meatal stenosis
   - Bladder neck obstruction
   - Ureteropelvic junction narrowing or obstruction
   - Severe vesicoureteral reflux
2. **Urinary calculi**
3. **Benign prostatic hypertrophy**
4. **Tumors**
   - Carcinoma of the prostate
   - Bladder tumors
   - Retroperitoneal lymphoma
   - Carcinoma of the cervix or uterus
5. **Inflammation**
   - Prostatitis
   - Ureteritis
   - Urethritis
   - Retroperitoneal fibrosis
6. **Sloughed renal papilla or blood clots**
7. **Pregnancy**
8. **Uterine prolapse and cystocele**
9. **Functional disorders**
   - Neurogenic (spinal cord damage or diabetic nephropathy)
   - Other functional abnormalities of the ureter or bladder (often termed *dysfunctional obstruction*).



(Ref: Robbins/10th/945)

Nephritic and Nephrotic Syndromes

Q. What do you mean by nephritic syndrome? (DU-21Ja,20Nv/M,09/08Ja, CMU-21M,15Ju, RU-20M,17/10Ja)

Q. Define nephritic syndrome / acute glomerulonephritis (AGN). (RMU-22M,03Ja)

Q. What are the causes of nephritic syndrome? (RU-20/19M,17Ju/M,10Ja)

Q. Short note: AGN. (BUP-22Nv, CU-12Ja)

Ans.

Nephritic syndrome / AGN: Nephritic syndrome or acute glomerulonephritis (AGN) is a **glomerular disease** of kidney which is characterized by **inflammation in the glomeruli** and is manifested as **haematuria** (red

blood cells and red cell casts in urine), **proteinuria** (usually subnephrotic range) with or without **edema, azotemia** and **hypertension.**

(Ref: Robbins/10th/906)

Causes of nephritic syndrome (AGN): *(Very Important for VIVA)*

A. PRIMARY GLOMERULAR DISEASES:

1. **Acute proliferative glomerulonephritis:**
   a. ***Post-streptococcal glomerulonephritis*** (Group A β-hemolytic streptococcus)
   b. ***Non-streptococcal acute glomerulonephritis*** (post-infectious glomerulonephritis)
      - **Bacterial:** Staphylococcal endocarditis, pneumococcal pneumonia, meningococcaemia.
      - **Viral:** Hepatitis-B & C virus, mums, HIV, varicella, infectious mononucleosis.
      - **Parasitic:** Malaria, toxoplasmosis.
2. Rapidly progressive (crescentic) glomerulonephritis (RPGN)
3. Membranoproliferative glomerulonephritis
4. IgA nephropathy

B. SYSTEMIC DISEASES:

1. Goodpasture syndrome (pulmonary hemorrhage associated with renal failure)
2. SLE (Lupus nephritis)
3. Polyarteritis nodosa
4. Wegener granulomatosis (granulomatosis with polyangiitis)
5. Microscopic polyangiitis
6. Henoch-Schönlein purpura
7. Cryoglobulinaemia.

(Ref: Robbins/10th/906; Harsh Mohan/7th/648)

Q. Mention the pathogenesis of AGN (acute glomerulonephritis). (DU-19Nv,08/05Ja, RU-08Ja)
Q. Mention the pathogenesis & pathology of acute diffuse glomerulonephritis. (RU-13/09Ja)
Q. Write in brief about acute diffuse proliferative glomerulonephritis. (RU-19/18Nv,16Ju, SU-15Ja)
Q. Discuss briefly the etiopathogenesis of acute post-streptococcal glomerulonephritis. (DU-22Nv,21Ja,20Nv/M,17Ja,12Ju,09Ja, RU-17Ju/M,14Ju, CU-13Ja)
Q. Discuss briefly about pathogenesis of glomerular diesase. (RU-15Ju)
Q. What are the different immune mechanisms involved in glomerular injury? Write down the pathogenesis of acute post-streptococcal glomerulonephritis. (DU-15Ju)
Ans.

Pathogenesis of AGN:

Post-streptococcal glomerulonephritis:

Causative agent: Group A β-hemolytic streptococcus (*Streptococcus pyogen*).

Past history: It usually appears 1 to 4 weeks after a sterptococcal infection of the pharynx *(sore throat)* or skin *(infected scabies / impetigo)*.

Pathogenesis: Post-streptococcal glomerulonephritis is an ***immunologically mediated*** disease.

- Following streptococcal infection, formation of antibody against **M-protein** of streptococcal cell wall → Formation of ***antigen-antibody complex*** in circulation → Deposition of Ag-Ab complex in glomeruli.
- Streptococcal antigen is settled in glomeruli → Formation of antibody & reaction of Ab with the settled streptococcal Ag in glomeruli.
- Release of enzyme (e.g. *proteinase*) from bacteria → enzyme causes alteration of glomerular basement membrane → Formation of Ab against the altered glomerular basement membrane → Ag-Ab reaction.

Antigen-antibody complexes, generated from the above mentioned processes, implanted in glomerular basement membrane

↓

Activation of complement pathway and formation of-

↓

Chemotactic factors → Aggregation of neutrophils & macrophages → Release of enzyme

Membrane attack complex (MAC)

↓

Injury to the epithelial, endothelial & mesangial cells

↓

Acute glomerulonephritis (AGN)

Non-poststreptococcal AGN (post-infectious glomerulonephritis):

1. **Bacterial:** Staphylococcal endocarditis, pneumococcal pneumonia, meningococcaemia.
2. **Viral:** Hepatitis-B & C virus, mums, HIV, varicella, infectious mononucleosis.
3. **Parasitic:** Malaria (e.g. *P. falciparum*), toxoplasmosis.

(Ref: Robbins/10th/906; Lecture SSMC)

Q. Write down the morphology of acute diffuse proliferative glomerulonephritis. (SU-14Ju)
Q. Mention the microscopic findings of acute diffuse proliferative glomerulonephritis. (SU-10Ju)
Q. Write the morphology of post-streptococcal AGN. (SU-19Nv,17M,16Ja)
Q. Give the morphology of AGN. (SU-20Nv)

Ans.

Morphology of acute diffuse proliferative glomerulonephritis (post-streptococcal AGN):

Macroscopic:

- Kidney is enlarged
- The surface is smooth, pale with red haemorrhagic spots scattered all over the surface

Microscopic:

- Enlarged, hypercellular glomeruli
- Combination of proliferation, swelling, and leukocyte infiltration obliterates the capillary lumens
- There may be interstitial edema and inflammation
- The tubules often contain red cell casts.

(Ref: Robbins/10th/908)

Q. Mention the clinical features of AGN.

Ans.

Clinical features of AGN:

1. Malaise
2. Fever (low-grade)
3. Nausea
4. Oliguria
5. Hematuria (smoky or cola-coloured urine)
6. Mild proteinuria (usually less than 1 gm/day)
7. Periorbital edema
8. Mild to moderate hypertension.

(Ref: Robbins/10th/909)

Q. Write down the complications of AGN. (DU-11Ju,05Ja)
Ans.

Complications of AGN: ***(Important for VIVA)***

1. Acute renal failure
2. Chronic glomerulonephritis
3. Chronic renal failure
4. Electrolyte and acid-base disturbance
   - Hyperkalaemia
   - Metabolic acidosis
   - Hyponatraemia
5. Hypertensive encephalopathy
6. Left ventricular failure
7. Papillary necrosis.

(Ref: Robbins/10th/909; Lecture DMC)

Q. Write down the prognosis of AGN.
Ans.

Prognosis of AGN:

1. **Children:** More than 95% eventually recover totally with conservative therapy. A small minority of children (<1%) become severely oliguric, and develop a rapidly progressive form of glomerulonephritis, and a few may progress to chronic glomerulonephritis (chronic renal failure).
2. **Adult:** About 60% recover promptly, some develop rapidly progressive glomerulonephritis and others chronic glomerulonephritis.

(Ref: Robbins/10th/909)

Q. Define nephrotic syndrome. (DU-23M,22Nv,17/16Ja,12Ju, CMU-22Nv, RMU-22M,20Nv/M,17/12/10Ja)
Q. Enumerate the causes of nephrotic syndrome. (DU-17M,16Ja,12Ju, CMU-22/20Nv,13Ju, RU-18M,16Ju,15/10/08Ja)
Q. Enumerate the primary causes of nephrotic syndrome. (SU-08Ja)
Q. Short note: Nephrotic syndrome. (DU-15Ja, RU-14Ja, CU-10Ju,09Ja)
Ans.

Nephrotic syndrome: It is a ***glomerular syndrome*** which is characterized by **massive proteinuria** (≥3.5 gm/day), **hypoalbuminaemia** (plasma albumin level < 3 gm/dl), **generalized edema, hyperlipidaemia** and **lipiduria** (lipid in the urine).

(Ref: Robbins/10th/896,912)

Fig: Patient of nephrotic syndrome.

Causes of nephrotic syndrome: ***(Very Important for VIVA)***

1. **Primary glomerular diseases:**
   - Minimal-change disease (*most common in children*)
   - Membranous glomerulonephritis (*most common in adults*)
   - Membranoproliferative glomerulonephritis
   - Focal segmental glomerulosclerosis

- IgA nephropathy

2. **Systemic diseases:**
   - Diabetes mellitus
   - Amyloidosis
   - Systemic lupus erythematosus (SLE)
   - Drugs (nonsteroidal anti-inflammatory, penicillamine, heroin)
   - Infections (malaria, syphilis, hepatitis B & C, HIV)
   - Malignancy (carcinoma, lymphoma, myeloma)
   - Miscellaneous (bee sting allergy, hereditary nephritis).

(Ref: Robbins/10th/912; Harsh Mohan/7th/648)

Nice to Know:

- In ***children, primary glomerulonephritis*** is the cause in majority of cases of the nephrotic syndrome; most frequent being ***minimal-change disease (lipoid nephrosis) (65%)***.
- In ***adults,*** on the other hand, ***systemic diseases*** (diabetes, amyloidosis and SLE) are more frequent causes of nephritic syndrome. The most common primary glomerular disease in adults is ***membranous glomerulonephritis (40%)***.

(Ref: Harsh Mohan/7th/648)

Q. Write down the urinary findings in a case of AGN (DU-23Nv,21Ja,20Nv/M,16Ja,15/11/10Ju, CMU-23M) **and nephrotic syndrome.** (DU-23M,12Ja, SMU-23M,22Nv/M,10/09Ja, CMU-22Nv)
Q. Write down the laboratory investigations to differentiate AGN from nephrotic syndrome. (DU-17M)
Q. Mention the urinary findings of nephrotic and nephritic syndrome. (DU-14Ju, CU-20M, RU-11Ju)
Q. Differentiate between AGN and nephrotic syndrome in urinary findings. (CU-19/18Nv, SU-13Ju)
Q. How can you differentiate nephrotic and nephritic syndrome by examining urine? (RU-14/12Ju)
Q. Mention the urinary findings of AGN (DU-19Nv, RMU-23M, CU-14/13Ja, SU-11Ja) **and nephrotic syndrome.** (SU-11Ja, RU-11Ju)
Q. What are the expected urinary findings in a patient of nephritic syndrome? (DU-06Ja, U-15Ja, CU-12Ju)
Ans.
Urinary findings in nephritic syndrome (AGN) & nephrotic syndrome:

Examination	Nephritic syndrome (AGN)	Nephrotic syndrome
A. Physical		
1. Amount of urine	Markedly reduced (200-400 ml/day)	Reduced
2. Colour	High coloured (dark red or smoky)	Normal colour
3. Odour	Normal	Normal
4. Specific gravity	High	Normal / high
B. Chemical		
1. Reaction	Acidic	Acidic
2. Albumin	+/++ (moderate)	+++ /++++ (massive)
C. Microscopic		
1. RBC	Plenty	+ / -
2. Cast	RBC cast	Hyaline & granular cast
3. Epithelial cell & pus cell	May be present	May be present
4. Organism	Absent	Absent

(Ref: Prof. Khaleque/204; Harsh Mohan/7th/649; Lecture SSMC)

Q. Give the differences between nephritic syndrome (AGN) and nephrotic syndrome. (RMU-22/21/20Nv, CMU-22/21Nv,15Ju, SU-18M,15Ja)

Ans.

Differences between nephritic syndrome (AGN) and nephrotic syndrome: ***(****V.V.I. for VIVA)***

Traits	Nephritic syndrome (AGN)	Nephrotic syndrome
1. Onset	Sudden	Gradual
2. Age group	5-12 years	2-6 years
3. History	Recent *Streptococcal* infection (e.g. sore throat or skin infection)	No such history
4. Edema	Mild (puffy face, ankle edema)	Generalized edema
5. Ascites	Unlikely	Likely
6. Urine colour	High colour / smoky	Normal colour
7. Urine RME	RBC, RBC cast	Hyaline & granular cast
8. Proteinurea	Mild (<1 gm/day)	Massive (≥ 3.5 gm/day)
9. Hematuria	Present (microscopic)	Absent
10. Oliguria	Present	Present in advanced disease
11. Lipiduria	Absent	Present
12. Hyperlipidaemia	Absent	Present
13. Hypoalbuminaemia	Uncommon	Present (plasma albumin level < 3 gm/dl)
14. Hypercoagulability	Absent	Present

(Ref: Robbins/9th/906,911; Harsh Mohan/7th/649; Lecture SSMC & DMC)

Q. A boy of 10 years has recently developed periorbital oedema. He had a history of sore throat two weeks prior to development of oedema. What is your likely diagnosis? What are the macroscopic & microscopic urinary findings of that case? (DU-23Nv)

Q. A boy of 11 years presented with puffiness efface and scanty reddish mivturition for last few days. He also gives H/O sore throat few weeks back. What is your provisional diagnosis? Mention the urinary findings of the patient. (BUP-19/18M)

Q. A boy of 11 years suddenly develops puffiness of face with scant high coloured urine formation. He gives history of sore throat about 3 weeks back. What is the likely diagnosis? Give the positive findings of his routine urine examination test. (DU-17Nv)

Ans.

Provisional diagnosis: Acute glomerulonephritis (post-streptococcal).

Positive findings in routine urine examination test:

a. **Physical**
   - **Amount of urine:** Markedly reduced.
   - **Colour:** High coloured (dark red/ smoky).
   - **Specific gravity:** High.

b. **Chemical**
   - **Reaction:** Acidic.
   - **Albumin:** + / ++.

c. **Microscopic**
   - **RBC:** Plenty.
   - **Cast:** RBC cast.
   - **Epithelial cell:** (+).

Q. A boy of 7 years developed periorbital edema with high coloured scanty urination following a history of sore throat 3 weeks back. What is your clinical diagnosis? What do you expect in microscopic findings of his urine? (DU-14Ja)

Ans.

Clinical diagnosis: Acute glomerulonephritis (post-streptococcal).

Microscopic findings in urine:

- RBC (dysmorphic RBC)
- RBC cast.

Q. A boy of 10 years has presented with fever, peri-orbital edema, and oliguria. What is your diagnosis? What are the possible urinary findings in this case? (RMU-21M)

Ans.

Provisional diagnosis: Acute glomerulonephritis (post-streptococcal).

Possible urinary findings: *Please write from above.*

Q. A boy of 10 years presented with fever, peiorbital oedema & oliguria. What is your diagnosis? What are the investigations to be done & give the possible urinary findings in this case? (RMU-23M)

Q. A boy of 13 years has presented with oliguria and periorbital edema. What is your provisional diagnosis? How you will diagnose the case? (DU-10Ja)

Q. What are the investigations to be done to diagnose a case of acute glomerular nephritis (AGN)? (RMU-23M)

Q. Give the laboratory findings in nephritic syndrome. (RU-13Ju)

Ans.

Provisional diagnosis: Acute glomerulonephritis (AGN).

*{**Note:** It's most important D/D is nephrotic syndrome. But in that case the age would be 2-6 years, oliguria will be absent and edema should be generalized rather that periorbital edema}*

Diagnosis:

1. **History taking**
2. **Physical examination**
3. **Investigations:**
   - **A.** ***Urine examination (Urine R/M/E):***
     - **a. Physical**
       - **Amount of urine:** Markedly reduced.
       - **Colour:** High coloured (dark red/ smoky).
       - **Odour:** Normal /pungent.
       - **Specific gravity:** High.
     - **b. Chemical**
       - **Reaction:** Acidic.
       - **Albumin:** (+ / ++) {+++ / ++++ in case of nephrotic syndrome}
     - **c. Microscopic**
       - **RBC:** Plenty.
       - **Cast:** Presence of RBC cast.
       - **Epithelial cell:** (+)

- **Pus cell:** Normal.
- **Organism:** Absent.

B. *Complete blood count (CBC):*
   - Polymorphonuclear leukocytosis
   - Normocytic normochromic anemia may be present

C. *Serum C_3 level:* Reduced.

D. *Evidence of streptococcal infection:* Raised ASO titer

E. *Renal biopsy:* Usually not required (required only in atypical presentation).

Q. A child of 10 years has presented with hematuria, oliguria and history of scabies two weeks ago. What is your provisional diagnosis? *(Important for VIVA)*

Ans.

Provisional diagnosis: Acute glomerulonephritis (AGN).

Q. A boy of 10 years passes 10 gm protein per day. Serum albumin 25 gm/L. What is your provisional diagnosis? *(Important for VIVA)*

Ans.

Provisional diagnosis: Nephrotic syndrome.

Q. A boy of 10 years presented with generalized edema, Low serum albumin and massive proteinuria. Renal biopsy of kidney shows no significant changes in glomerulus (light microscopy). What is your diagnosis? What are other relevant investigations should be done?

Q. Discuss the laboratory findings in nephrotic syndrome. (RU-13Ju)

Ans.

Diagnosis: Nephrotic syndrome *(minimal change disease)*.

Investigations:

- Routine and microscopic examination (R/M/E) of urine:
  - Massive proteinuria (albumin + + +/ + + + +)
  - Cast: Hyaline & granular casts may be present
- 24 hours urinary total protein (>3.5 gm)
- Albumin/globulin ratio - reduced
- Serum cholesterol & triglyceride level – increased
- Serum C_3 – normal
- Total serum calcium level- decreased
- Renal biopsy (in suitable cases).

Q. A 12 years old child having puffiness in the face and oliguria. Write the possible causes and how will you investigate for the diagnosis? (CU-20Ju)

Q. A boy of 10 years presented with oliguria and edema. What are the possible causes? How will you proceed to diagnose the case in the laboratory? (CU-17M,14Ju)

Ans.

Possible causes:

1. Nephritic syndrome (AGN)
2. Nephrotic syndrome.

Laboratory diagnosis: *Please write from above.*

Q. Write in short about lipoid nephrosis (RU-07Ja)**/ minimal change disease.** (RU-18M)
Q. Short note: Minimal change disease. (RU-17M,10Ja)
Ans.
Minimal change disease (lipoid nephrosis): Minimal change disease (lipoid nephrosis) is seen most often in **young children** but can also occur in older children and adults. It is the prototype of the **nephrotic syndrome.**

It is characterized by ***diffuse effacement of foot processes of epithelial cells (podocytes)*** in glomeruli that appear virtually normal by light microscopy.

The peak incidence is between **2 and 6 years** of age. The most characteristic feature of this condition is the **dramatic response to *corticosteroid* therapy.**

Etiology & pathogenesis: It involves some immune dysfunction, eventually resulting in the elaboration of a ***cytokine*** that damages ***visceral epithelial cells (podocytes)*** and cause ***proteinuria.*** The ultrastructural changes point to a primary *visceral epithelial cell injury*, and ***loss of glomerular polyanions***. Thus, defects in the charge barrier may contribute to the ***proteinuria.***

Morphology:

Macroscopic: Kidney tends to be pale or even yellowish in colour and slightly larger & heavier than normal.

Microscopic:

- No visible basement membrane changes;
- Fused foot processes of podocytes;
- Lipid accumulation in renal tubular cells.

Prognosis: Despite massive proteinuria, renal function remains good, and the long term prognosis is excellent for children and adults.

(Ref: Robbins/10th/914; BRS Pathology/5th/265)

Q. Why minimal change disease is called lipoid nephrosis?
Ans.
Minimal change disease is called lipoid nephrosis: The cells of the proximal tubules are often laden with lipid and protein, reflecting tubular reabsorption of lipoproteins passing through diseased glomeruli, thus the historical term **lipod nephrosis.**

(Ref: Robbins/10th/914)

Q. What is membranous nephropathy / glomerulonephropathy?
Q. Write the morphology of membranous glomerulonephropathy. (SU-08Ja)
Ans.
Membranous nephropathy / glomerulonephropathy: Membranous nephropathy is a common cause of the nephrotic syndrome in adults. It is characterized by diffuse thickening of the glomerular capillary wall due to the accumulation of deposits containing Ig along the subepithelial side of the basement membrane.

(Ref: Robbins/10th/912)

Morphology:

- **Light microscopy:** Uniform diffuse thickening of the glomerular capillary wall.
- **Electron microscopy:** Basement membrane markedly thickened by intramembranous and epimembranous (subepithelial) immune complex deposits appearing as irregular spikes protruding from the GBM (**"spike and dome"** appearance).
- **Immunofluorescence microscopy:** Shows granular deposits of immunoglobulins and various amount of complement along the GBM.

(Ref: Robbins/10th/913; BRS Pathology/5th/265)

Q Short note: IgA nephropathy.
Ans.

- **Pus cell:** Normal.
- **Organism:** Absent.

B. ***Complete blood count (CBC):***
   - Polymorphonuclear leukocytosis
   - Normocytic normochromic anemia may be present

C. ***Serum C_3 level:*** Reduced.

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Ans.

Diagnosis: Nephrotic syndrome *(minimal change disease)*.

Investigations:

- Routine and microscopic examination (R/M/E) of urine:
  - Massive proteinuria (albumin +++/++++)
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Ans.

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2. Nephrotic syndrome.

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(Ref: Robbins/10th/913; BRS Pathology/5th/265)

Q Short note: IgA nephropathy.
Ans.

IgA nephropathy (Berger disease): IgA nephropathy is one of the **most common** causes of recurrent microscopic or gross hematuria and is the **most common** glomerular disease worldwide which is characterized by the **deposition of IgA** in the **mesangium**.

Pathogenesis:

A genetic or acquired abnormality of immune system
↓
Increased IgA synthesis in response to respiratory or gastrointestinal response to environmental agents (virus, bacteria, food protein)
↓
Ig A_1 and Ig A_1 containing immune complexes are then trapped in the mesangium
↓
Activation of alternate complement pathway
↓
Glomerular injury.

(Ref: Robbins/10th/920)

Q. What are the causes of chronic glomerulonephritis?

Ans.

Chronic glomerulonephritis: Chronic glomerulonephritis refers to **end-stage glomerular disease** that may result from specific types of glomerulonephritis or may develop without antecedent history of any of the well-recognized forms of acute glomerulonephritis.

Primary glomerular disease that leads to chronic glomerulonephritis are-

1. Post-streptococcal
2. Rapidly progressive glomerulonephritis (RPGN)
3. Membranous nephropathy
4. Membranoproliferative glomerulonephritis (MPGN)
5. IgA nephropathy
6. Focal segmental glomerulosclerosis (FSGS).

(Ref: Robbins/9th/925)

Q. Short note: Diabetic nephropathy. (SU-05M)

Ans.

Diabetic nephropathy: The term **diabetic nephropathy** is applied to the conglomerate of lesions that often occur concurrently in the **diabetic kidney**. It is one of the leading causes of **chronic kidney failure**.

Advanced or end stage kidney disease occurs in as many as 40% of both insulin dependent type 1 diabetes and type 2 diabetes.

Glomerular syndromes occur in diabetic nephropathy: By far the most common lesions involve the glomeruli and are associated clinically with three glomerular syndromes-

1. Non-nephrotic proteinuria
2. Nephrotic syndrome and
3. Chronic renal failure.

However, diabetes also affects the arterioles (causing hyalinizing arteriolar sclerosis), increases susceptibility to the development of pyelonephritis and particularly papillary necrosis, and causes a variety of tubular lesions.

Lesions caused by diabetic nephropathy: Three lesions are encountered-

1. Glomerular lesions
2. Renal vascular lesions, principally arteriosclerosis;
3. Pyelonephritis, including necrotizing papillitis.

Morphology:

- Basement membrane markedly thickened;
- Diffuse or nodular mesangial accumulations of basement membrane-like material.

(Ref: Robbins/10th/923,1118; BRS Pathology/5th/265)

Tubular and Interstitial Diseases

Q. Give the pathogenesis of acute tubular injury (ATI) / acute tubular necrosis (ATN).
Q. Give the pathogenesis of acute renal failure in acute tubular necrosis.
Q. Short note: Acute tubular necrosis.
Ans.
Acute tubular injury (ATI) / acute tubular necrosis (ATN): Acute tubular injury (ATI) is a clinicopathologic entity characterized by ***damage to tubular epithelial cells*** and an ***acute decline in renal function***, often associated with **shedding of granular casts** and **tubular cells into the urine.**
It is the most common cause of acute kidney injury (AKI) and may produce oliguria (defined as urine output of <400 mL/day).

(Ref: Robbins BASIC PATHOLOGY/10th/567,568)

Types and causes:

1. **Ischaemic ATI** (due to decreased or interrupted blood flow):
   - Hypotension and shock *(hypovolemic shock)*
   - Severe trauma
   - Acute pancreatitis
   - *Hemolytic uremic syndrome (HUS)*
   - *Thrombotic thrombocytopenic purpura (TTP)*
   - Disseminated intravascular coagulation (DIC)
2. **Nephrotoxic ATI** (due to direct toxic injury to the tubules):
   - Drugs (such as gentamycin and other antibiotics)
   - Radiographic contrast agents
   - Poisons including heavy metals (e.g. mercury)
   - Organic solvents (e.g. carbon tetrachloride)
3. **Combined ischaemic & nephrotoxic ATI:**
   - Haemoglobinuria *(mismatched blood transfusion and other hemolytic crises)*
   - Myoglobinuria *(due to severe skeletal muscle injuries).*

(Ref: Robbins BASIC PATHOLOGY/10th/562)

Clinical features:
- Electrolyte abnormalities
- Acidosis
- Uremia
- Signs of fluid overload, often with oliguria.

(Ref: Robbins BASIC PATHOLOGY/10th/569)

Pathogenesis: The critical events in both ischemic and nephrotoxic ATI are believed to be-
1. Tubular injury &
2. Persistent and severe disturbances in blood flow.

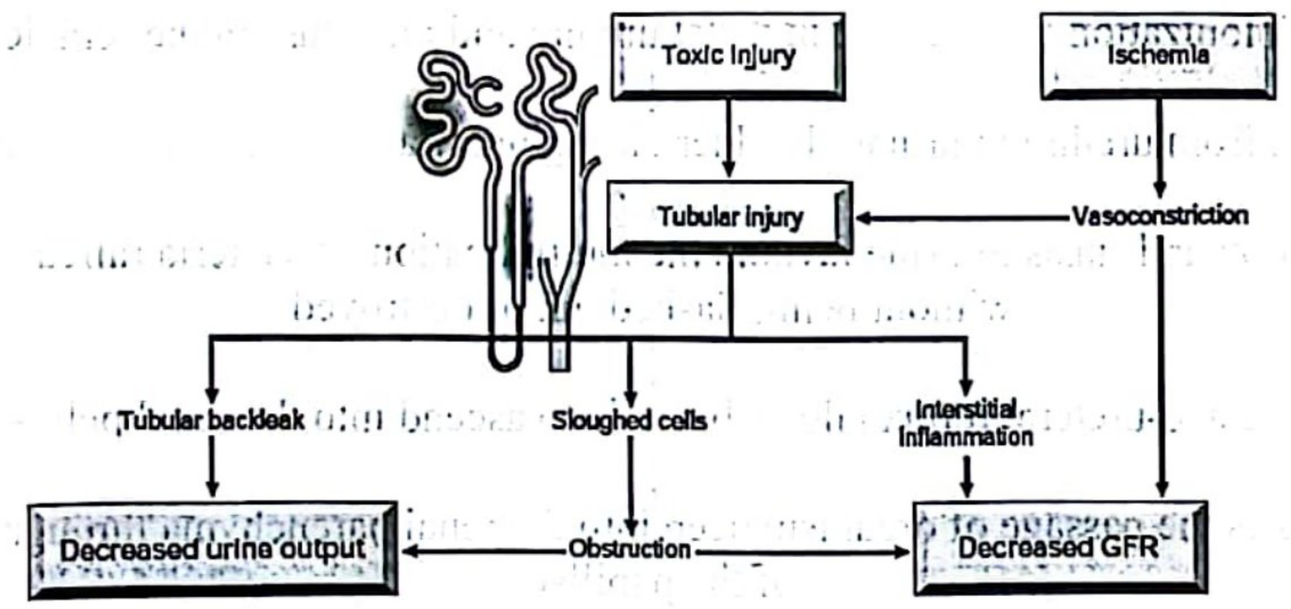


Fig: Postulated sequence in ischemic or toxic acute tubular injury.

Morphology: Injury or necrosis of segments of the tubules (typically the proximal tubules), proteinaceous casts in distal tubules, and interstitial edema

(Ref: Robbins BASIC PATHOLOGY/10th/569 + 10th/924)

Q. Define pyelonephritis. (DU-11Ja) **Mention its types.**

Q. Short note: Pyelonephritis. ***(For VIVA)***

Ans.

Pyelonephritis: Pyelonephritis is defined as **inflammation affecting the tubules, interstitium, and renal pelvis.** It is one of the most common diseases of the kidney.

Types: It occurs in *two* forms-

1. **Acute pyelonephritis** - is generally caused by bacterial infection and is associated with urinary tract infection (UTI).
2. **Chronic pyelonephritis** - is a more complex disorder; bacterial infection plays a dominant role, but other factors (vesicoureteral reflux, obstruction) predispose to repeat episodes of acute pyelonephritis.

(Ref: Robbins/10th/927)

Etiology:

1. *E. coli* (most common)
2. *Proteus*
3. *Klebsella*
4. *Enterobacter*
5. *Streptococcus fecalis*
6. *Staphylococci*
7. Polyoma virus
8. Cytomegalovirus
9. Adenovirus.

Routes of infection: There are two routes by which bacteria can reach the kidneys:

1. Through the bloodstream (haematogenous infection)
2. From the lower urinary tract (ascending infection) - most common.

(Ref: Robbins/10th/927)

Q. Write in short the pathogenesis of ascending infection in pyelonephritis. (DU-11Ja) ***(For VIVA)***

Ans.

Pathogenesis of ascending infection in pyelonephritis:

Common agents for ascending infection in pyelonephritis:

- *E. coli*
- *Proteus*
- *Enterobacter.*

Pathogenesis:

Colonization of organism in distal urethra and introitus (in the female)

↓

Entrance of organism from urethra to urinary bladder during urethral catheterization or other instrumentation

↓

Urinary tract obstruction and stasis of urine favours the multiplication of bacteria (already within the bladder) without being flashed out or destroyed

↓

Vesico-ureteral reflux allows bacteria to ascend into the renal pelvis

↓

Intra-renal reflux, allows the passage of organism deep into the renal parenchyma through open ducts at the tip of the papillae.

(Ref: Robbins/10th/927)

Q. Define acute pyelonephritis. What are the predisposing factors for acute pyelonephritis?
Ans.

Acute pyelonephritis: Acute pyelonephritis is a **suppurative inflammation of the kidney** caused by bacterial and sometimes viral (e.g. polyomavirus) infection, which can reach the kidney by hematogenous spread or, more commonly, through the ureters in association with vesicoureteral reflux.

(Ref: Robbins/10th/928)

Predisposing factors for acute pyelonephritis: Acute pyelonephritis is often associated with the following:

1. *Urinary tract obstruction*, either congenital or acquired
2. *Instrumentation* of the urinary tract, most commonly catheterization
3. *Vesicoureteral reflux*
4. *Pregnancy*
5. *Gender and age:* Females are more affected. But with increasing age the incidence in males rises as a result of prostatic hypertrophy and instrumentation
6. *Pre-existing renal lesions*
7. *Diabetes mellitus*
8. *Immuno-suppression and immunodeficiency.*

(Ref: Robbins/10th/928)

Q. What are the complications of acute pyelonephritis? (DU-11Ja)
Ans.

Complications of acute pyelonephritis:

a) **Papillary necrosis** (mainly in diabetics, sickle cell disease, and in those with urinary tract obstruction)
b) **Pyonephrosis** (when there is total or almost complete obstruction, particularly when it is high in the urinary tract)
c) **Perinephric abscess.**

(Ref: Robbins/10th/930)

Q. Give the urinary findings of pyelonephritis. *(Important for VIVA)*
Ans.

Urinary findings of pyelonephritis: *(Important for VIVA)*

- ***Acute pyelonephritis*:**
  - **Protein:** Trace amount
  - **Microscopically:** Many leucocytes (pyuria); leucocyte casts, typically rich in neutrophil (pus casts); some red cells, epithelial cells, and bacteria (bactereuria)
  - **Urine culture:** Positive for the organism
- ***Chronic pyelonephritis*:**
  - Protein in small amount, and
  - Pus cell.

(Ref: Robbins/10th/927-9310; Prof. Khaleque/120)

Q. Define UTI. Mention its type and causes.
Q. Why UTI is more common in female? (DU-09Ju)
Q. Short note: UTI.
Ans.

UTI: Presence and multiplication of bacteria in the urinary tract is called UTI.

Types:

1. **Upper tract infection-**
   - Parenchyma of kidney
   - Pelvis of kidney

2. **Lower tract infection-**
   - Bladder

Common / probable pathogens:

1. **Gram negative bacteria:**
   - E. *coli* (80-90% E. coli in young female)
   - Proteus
   - Pseudomonas
   - Klebsella

2. **Gram positive bacteria:**
   - S. *saprophyticus* (young female)
   - S. *epidermidis* (prosthetic device)
   - S. *aureus*
   - E. *fecalis*
   - E. *figium*

3. **Other bacteria:**
   - Mycobacterium tuberculosis
   - Clamydia
   - Mycoplasma
   - Leptospira

4. **Fungus:** Candida

5. **Parasite:**
   - T. *vaginalis*
   - E. *vermicularis*
   - S. *hematobium*
   - W. *bancrofti*

(Ref: Robbins/8th/939; Microbiology Lecture, SSMC)

UTI is common in female: Because of-

- Shorter urethra.
- Absence of antibacterial properties such as are found in prostatic fluid
- Close proximity with anus.
- Hormonal change affecting adherence of bacteria to the mucosa.
- Urethral trauma during sexual intercourse.

(Ref: Robbins/8th/939; Microbiology Lecture, SSMC)

Acute and Chronic Renal Failure

Q. List the causes of acute renal failure. (DU-11Ju)
Q. Short note: Acute renal failure / acute kidney injury.
Ans.

Acute renal failure (ARF) / acute kidney injury (AKI): It refers to a sudden and usually reversible loss of renal function, which usually develops over days or weeks and usually accompanied by a reduction in urine volume.

(Ref: Davidson/21st/482)

Or,

Acute renal failure / acute kidney injury is characterized by rapid decline in GFR (within hours to days), with concurrent dysregulation of fluid and electrolyte balance, and retention of metabolic waste products normally excreted by the kidney including urea and creatinine.

(Ref: Robbins/10th/898)

Causes of acute renal failure:

a) **Pre-renal causes:**
   1) ***Systemic:***
      - Heart failure
      - Blood or fluid loss
   2) ***Local:***
      - Renal artery occlusion / stenosis
      - Diseases affecting arterioles

b) **Renal causes:**
   1) Acute tubular necrosis (ATN) / toxic / septic renal failure: 85%
   2) Glomerular disease:
      - Primary
      - Component of systemic disease
   3) Interstitial disease

c) **Post-renal causes:** Obstruction e.g. stones, tumour, prostatic enlargement.

(Ref: Davidson/21st/482,483)

Stages of acute renal failure: It can be divided into **three** stages-

1. **Initiating stage**
2. **Maintenance stage-** Oliguria, uraemia, progressive rise of blood creatinine, hyperkalemia, metabolic acidosis with salt and water overload.
3. **Recovery stage-** Gradual increase in urine volume, may be 3 liters per day. Blood urea and creatinine levels begin to return to normal.

(Ref: Prof. Khaleque/123)

Q. A girl of 6 years has presented with history of passage of watery stool few times and has developed cessation of maturation subsequently. What are the most likely mechanisms involved? (DU-08Ja)

Ans.

Acute watery diarrhoea
↓
Loss of plenty of fluid
↓
Acute hypovolaemia
↓
Several auto regulation mechanisms come into play
↓
When persistent hypovolemia is present, these mechanisms fail
↓
There is severe prolonged under perfusion of kidneys and acute decline of GFR producing low volume highly concentrated urine
↓
More severe and persistent hypovolaemia
↓
Acute tubular necrosis (ATN)
↓
Acute renal failure
↓
Cessation of micturition.

Q. What is chronic renal failure (CRF) / chronic kidney disease (CKD)? What are the causes of CRF/CKD?

Ans.

Chronic renal failure (CRF) / chronic kidney disease (CKD): It refers to an irreversible deterioration in renal function which classically develops over a period of years.

Or,

Chronic kidney disease (previously called chronic renal failure) is defined as the presence of a diminished GFR that is persistently less than 60 mL/minute/1.73 m^2 for at least 3 months, from any cause, and/or persistent albuminuria.

(Ref: Robbins/10th/898)

Causes of CRF/CKD:

1) Diabetes mellitus (20 - 40%)
2) Interstitial diseases (20 - 30%)
3) Glomerular diseases (10 - 20%) e.g. IgA nephropathy is most common
4) Hypertension (5 - 20%)
5) Systemic inflammatory diseases (5 - 10%) e.g. SLE, vasculitis
6) Congenital and inherited (5%) e.g. polycystic kidney disease, Alport's syndrome
7) Renal artery stenosis (5%)
8) Unknown (5 - 20%).

(Ref: Davidson/21st/487)

Kidney Tumors

Q. Classify kidney tumours. (DU-10Ja, CU-20M, RU-18/08Ja)

Ans.

Kidney tumors: ***(Important for VIVA)***

1. **Benign:**
   - Renal papillary adenoma
   - Angiomyolipoma
   - Oncocytoma
2. **Malignant:**
   - **Renal cell carcinoma (*adenocarcinoma* of the kidney):**
     - Clear cell carcinoma (most common, 65%)
     - Papillary renal cell carcinoma (10-15%)
     - Chromophobe renal carcinoma (5%)
   - **Urothelial carcinomas of the renal pelvis**
   - **Wilms tumour (*nephroblastoma*).**

(Ref: Robbins BASIC PATHOLOGY/10th/578-580 + 10th/948)

Q. Write the morphology of renal cell carcinoma. (DU-10Ja)

Q. Write the microscopic findings of renal cell carcinoma.

Q. Short note: Renal cell carcinoma. (DU-07Ju,05S)

Ans.

Renal cell carcinoma (adenocarcinoma of the kidney): Renal cell carcinomas are derived from the renal tubular epithelium (adenocarcinoma of the kidney), and represent 80% to 85% of all primary malignant neoplasms of the kidney and 2% to 3% of all cancers in adults.

Classification: It is of 3 types - clear cell carcinoma, papillary renal cell carcinoma, chromophobe renal carcinoma.

Morphology:

***Macroscopic*:**

1. The tumour may arise in any portion of the kidney, but more commonly affects the poles.
2. ***Clear cell carcinomas*** arise most likely from proximal tubular epithelium, and usually occur as solitary unilateral lesions. They are spherical masses of varying size and composed of **yellow to orange to gray-white** tissue, with prominent areas of **cystic softening** or of **hemorrhage,** either fresh or old.
3. ***Papillary renal cell carcinomas*** arise from distal convoluted tubules, and have gross evidence of necrosis, hemorrhage, and cystic degeneration. They tend to be bilateral and multiple.
4. ***Chromophobe-type renal cell carcinoma*** tends to be grossly tan-brown.

***Microscopic*:**

1. **Clear cell carcinoma (65%):** Cells are rounded or polygonal shape. Abundant ***clear*** or granular cytoplasm.
2. **Papillary renal cell carcinoma (10-15%):** Composed of cuboidal or low columnar cells arranged in ***papilla formation*** with ***fibrovascular cores***. The cells may have a clear or, more commonly, pink cytoplasm.
3. **Chromophobe renal carcinoma (5%):** It is made up of cells having clear, flocculent cytoplasm with very prominent, distinct cell membranes. The nuclei are surrounded by halos of clear cytoplasm.

(Ref: Robbins BASIC PATHOLOGY/10th/578-580 + 10th/950)

Fig: Renal cell carcinoma.

Q. What are the risk factors / causes of renal cell carcinoma?

Ans.

Risk factors / causes of renal cell carcinoma:

1. Tobacco smoking
2. Male gender
3. Obesity (particularly in women)
4. Hypertension
5. Unopposed estrogen therapy
6. Exposure to asbestos, petroleum products, and heavy metals
7. Patients with ESRD, chronic kidney disease, acquired cystic disease, and tuberous sclerosis.

(Ref: Robbins BASIC PATHOLOGY/10th/578,579 + 10th/948)

Q. Write the clinical features / diagnostic features of renal cell carcinoma.

Ans.

Clinical features of renal cell carcinoma: *(Very Important for VIVA)*

1. Hematuria (occurring in >50% of cases)
2. Costovertebral (flank) pain and a palpable mass
3. Generalized constitutional symptoms (such as fever, malaise, weakness and weight loss)

4. Polycythemia
5. Paraneoplastic syndromes (including hypercalcemia, hypertension, Cushing syndrome, or feminization or masculinization)
6. Wide metastases to the lungs & bones, followed in order by the regional lymph nodes, liver, adrenals, and brain.

It must be apparent that renal cell carcinoma manifests in many ways, some quite devious, but the ***triad*** of ***painless hematuria***, a ***palpable abdominal mass***, and dull ***flank pain*** is characteristic.

(Ref: Robbins BASIC PATHOLOGY/10th/580 + 10th/950)

Q. A male of 55 years presented with hematuria, loin pain and a palpable mass in the lumbar region of abdomen. What is the likely diagnosis? What are the histologic types of this lesion? (DU-18M)

Ans.

Likely diagnosis: Renal cell carcinoma.

Histologic types: *Please write from above.*

Q. A 40 years male presented with right flank colicky pain with hematuria. (CMU-22M)
a) Write your possible diagnosis?
b) What are the possible causes of it?
c) What are the laboratory tests and positive findings to establish the diagnosis?
Q. A 65 year old male having haematuria with loin pain. Radiology shows a right renal mass. Write your possible diagnosis & how will you investigate for diagnosis? (CU-18M)

Ans.

Possible diagnosis: Renal cell carcinoma.

Causes: *Please write from above.*

Laboratory investigations:

- Urine examination
  - Routine – RBC
  - Cytology – Malignant cells may be present
- Blood urea, serum creatinine – To see renal functional status.
- USG of whole abdomen
- Intravenous urography (IVU)
- Plain X-ray of KUB region – may show calcification
- Contrast CT scan of abdomen
- Chest x-ray / CT scan of chest – to detect lung metastasis (cannon ball)
- Isotope renogram – to see functional status of the kidneys
- Isotope bone scan – to detect bone metastasis.

Q. A 60 years old male presented with a mass in right loin having painless hematuria. What is the probable diagnosis? How you will confirm it? (DU-09Ju)
Q. A 50 years old female with a left loin mass having painless hematuria. What is your probable diagnosis? How will you confirm your diagnosis? (CU-19M)

Ans.

Probable diagnosis: Renal cell carcinoma.

Laboratory investigations: *Please write from the above question.*

Q. Short note: Wilms tumour / nephroblastoma. (DU-06M,04Ja, CMU-23M, SU-05/03Ja)

Ans.

Wilms tumour: It is the most common primary renal tumour of childhood. It occurs usually between 2 to 5 years of age. Approximately 5-10% of Wilms tumor involve both kidneys, either simultaneously or one after the other.

Pathogenesis:

- Wilms tumour associated gene is located at chromosome 11p13.
- The risk of Wilms tumour is increased in association with three congenital malformations:
  1. WAGR syndrome
  2. Denys-Drash syndrome
  3. Beckwith-Wiedemann syndrome

Morphology:

***Gross*:**

- A large, solitary, well-circumscribed mass.
- 10% are either bilateral or multicentric at the time of diagnosis.
- On cut section, the tumour is soft, homogenous, and tan to grey with occasional foci of haemorrhage, cyst formation and necrosis.

***Microscopic*:**

- Different stages of nephrogenesis.
- The classic triphasic combination of blastemal, stromal, and epithelial cell types is observed in the vast majority of lesions.
- Epithelial differentiation is usually in the form of abortive tubules or glomeruli.
- Stromal cells are usually fibrotic or mixoid in nature, although skeletal muscle differentiation is not uncommon.
- Rarely, other heterologous elements are identified, including squamous or mucinous epithelium, smooth muscle, adipose tissue, cartilage, and osteoid and neurogenic tissue.
- Approximately 5 % of tumours reveal anaplasia.

(Ref: Robbins/10th/480)

Renal Stones

Q. Mention the types of renal stones. ***(Very Important for VIVA)***

Q. What is staghorn calculi?

Ans.

Types of renal stone: There are four main types of renal calculi-

1. **Calcium oxalate and phosphate stones:** Most stones (about 70%) are calcium containing, composed largely of calcium oxalate or calcium oxalate mixed with calcium phosphate.

2. **Magnesium ammonium phosphate stones (triple stones or struvite stones)** (about 15%)**:** Formed largely after infection by urea-splitting bacteria (e.g. *proteus* and some staphyllococci), which convert urea to ammonia. The resultant ***alkaline urine*** causes the precipitation of magnesium ammonium phosphate salts. These form some of the largest stones, as the amounts of urea excreted are normally huge. Indeed, so-called **staghorn calculi** occupying large portions of the renal pelvis are almost always a consequence of infection.

3. **Uric acid stones** (5% to 10%)**:** Common in patients with hyperuricemia, such as gout.

4. **Cystine stones** (1% to 2%)**:** Caused by genetic defect in the renal reabsorption of amino acids, including cystine, leading to cystinuria.

(Ref: Robbins BASIC PATHOLOGY/10th/576 + 10th/947)

Q. What are the common causes of renal stone?

Ans.

Common causes of renal stone:

1. Gout
2. Hypercalceuria
3. Hypercalcaemia
4. Cystinuria
5. Primary hyperoxaluria
6. Hypercholesterolemia.

(Ref: Robbins/10th/947)

Q. Who are most affected in renal calculi?

Ans.

Most affected persons in renal calculi:

1. Men are affected more often than women.
2. Peak age at onset is between 20 and 30 years.
3. Familial and hereditary predisposition.
4. Inborn errors of metabolism, such as gout, cystinuria, and primary hyperoxaluria etc.

(Ref: Robbins/10th/947)

Urinary Bladder

Q. Short note: Acute and chronic cystitis.

Ans.

Acute and chronic cystitis:

Etiologic agents:

1. **Coliform bacteria:**
   - E. *coli*
   - Proteus
   - Klebsiella
   - Enterobacter
   - Tuberculous cystitis
   - Chlamydia
   - Mycoplasma
2. **Fungus:**
   - Candida albicans
   - Schistosoma haematobium
3. **Virus:**
   - Adenovirus

Predisposing factors:

1. Bladder calculi
2. Urinary obstruction
3. Diabetes mellitus
4. Instrumentation
5. Immunodeficiency
6. Radiation cystitis

Symptoms: All forms of clinical cystitis are characterized by a **triad** of symptoms-

1. Frequency, which in acute cases, may necessitate urination every 15-20 minutes.
2. Lower abdominal pain localized over the bladder region or in the suprapubic region, and
3. Dysuria (pain or burning on urination).

(Ref: Robbins/10th/955)

Q. Mention the complications of urinary bladder calculus / stone. (RU-08Ja)

Ans.

Complications of urinary bladder calculus / stone:

1. Bladder outlet obstruction
2. Infection
3. Anuria and retention of urine
4. Haematuria
5. Chronic bladder dysfunction
6. Bladder cancer.

(Ref: Lecture SBMC)

Q. Mention the tumours of urinary bladder. ***(For VIVA)***

Ans.

Tumors of urinary bladder:

A. Primary tumors:

1. Urothelial (transitional) tumours
   - Noninvasive urothelial (transitional cell) tumors
   - Infiltrating urothelial carcinoma
   - Variants: nested, microcystic, micropapillary, plasmacytoid, sarcomatoid, giant cell, poorly differentiated, lipid-rich, and clear cell
2. Adenocarcinoma
3. Squamous cell carcinoma
4. Mixed carcinoma
5. Small cell carcinoma
6. Sarcomas.

B. Secondary tumors:

1. Direct extension from primary lesions in nearby organs, mainly the cervix, uterus, prostate, and rectum.
2. Lymphoma (as a component of systemic disease).

(Ref: Robbins/10th/957-962)

Q. What are the risk factors of bladder carcinoma? ***(For VIVA)***

Ans.

Risk factors of bladder carcinoma:

1. Cigarette smoking
2. Industrial exposure to aryl amines
3. *Schistosoma haematobium* infection (most common cause of *squamous cell* bladder carcinoma)
4. Long-term use of analgesics
5. Heavy long term exposure to cyclophosphamide (an immunosuppressive agent)
6. Prior exposure of the bladder to radiation.

(Ref: Robbins/10th/958)

CHAPTER 09

MALE GENITAL SYSTEM

Diseases of male genital tract:

1. **Penis:**
   a. **Congenital anomalies:**
      - Hypospadias and epispadias
      - Phimosis
   b. **Inflammations:**
      - Syphilis
      - Gonorrhea
      - Chancroid
      - Granuloma inguinale
      - Lymphogranuloma venereum
      - Genital herpes
      - Balanoposthitis (infection of the glans and prepuce caused by *Candida albicans*, anaerobic bacteria, *Gardnerella*, and pyogenic bacteria)
   c. **Tumors:**
      - Benign: Condyloma acuminatum
      - Malignant:
        - Squamous carcinoma in situ / penile intraepithelial neoplasia
        - Invasive squamous cell carcinoma
2. **Testis and Epididymis:** *Please see below.*
3. **Prostate:**
   a. **Inflammations:**
      - Acute and chronic bacterial prostatitis
      - Chronic abacterial prostatitis
      - Granulomatous prostatitis
      - Autoimmune prostatitis
   b. **Benign enlargement:** Benign prostatic hyperplasia (BPH) or nodular hyperplasia.

c. **Tumours:**

***Primary tumors*:**

- Adenocarcinoma of the prostate (most common)
- Miscellaneous tomours and tumour-like conditions
  - Ductal adenocarconoma
  - Small cell carcinoma (neuroendocrine carcinoma) of prostate

***Secondary tumors*:**

- Urothelial cancer.

(Ref: Robbins/10th/963-983)

Testis

Q. Classify testicular tumors / neoplasms. (DU-22Nv,21Oct/M,19/17M/Ja,15Ja,13Ju,12/08Ja, RMU-23/22/21M,20/19M,18/16Ja,14Ju,10Ja, SUST-21Nv,20M,19Nv,16Ja,11Ju/Ja, CU-20/17M, 12Ju,06S)
Q. Name testicular tumors. (BUP-22M)
Q. Name the germ cell tumours of testis. (DU-09Ju, RU-17M,09Ja, SU-09/08Ja)
Q. Name the diseases of testis.
Q. Short note: Classification of testicular tumour. (CU-18M)
Ans.

Diseases of testis:

1. **Congenital:**
   - Cryptorchidism (undescended testis) {most common}
   - Absence of one or both testes
   - Synorchism (fusion of the testis)
2. **Regressive changes:** Atrophy and decreased fertility.
3. **Inflammatory:**
   - Nonspecific epididymitis and orchitis
   - Granulomatous (autoimmune) orchitis
   - Infections e.g. gonorrhea, mumps, tuberculosis, syphilis.
4. **Vascular disorders:** Torsion.
5. **Tumors:**

Spermatic cord and paratesticular tumors:

***Benign*:**

- Lipomas
- Adenomatoid tumor

***Malignant*:**

- Rhabdomyosarcomas (in children)
- Liposarcomas (in adults)

Testicular tumors:

A) Germ cell tumors (95%):

a. ***Seminomatous tumors:***
   - Seminoma (most common testicular tumor- about 50%)
   - Spermatocytic seminoma

b. ***Non-seminomatous tumors:***
   - Embryonal carcinoma
   - Yolk sac tumor

- Choriocarcinoma
- Teratoma

c. ***Mixed tumors (mixtures of seminomatous and non-seminomatous components):*** *(60%)*
   - Embryonal carcinoma plus teratoma plus yolk sac tumor
   - Embryonal carcinoma plus seminoma
   - Embryonal carcinoma plus teratoma (terato-carcinoma)

B) Sex cord-stromal tumors:
- Leydig cell tumors
- Sertoli cell tumors (androblastoma)

C) Gonadoblastoma

D) Testicular lymphoma.

(Ref: Robbins/10th/966-974)

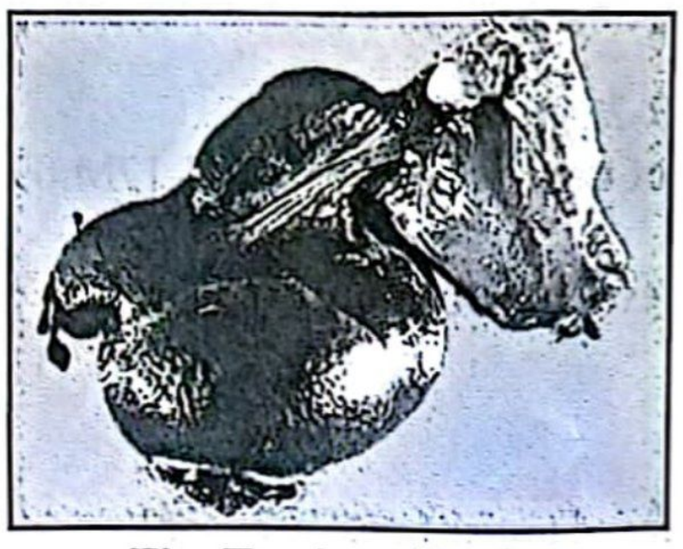


Fig: Torsion of testis.

Q. What is cryptorchidism? (DU-19M, RU-20M)
Q. Write in brief about cryptorchidism. (RMU-21Nv,19/17M)
Q. Short note: Cryptorchidism. (DU-11Ju, RMU-22Nv,18M,16/15/13Ju,11/10Ja)
Ans.
Cryptorchidism: Cryptorchidism is a complete or partial failure of the intra-abdominal testes to descend into the scrotal sac and is associated with testicular dysfunction and an increased risk of testicular cancer.

(Ref: Robbins/10th/966)

Or,

Cryptorchidism refers to incomplete descent of the testis from the abdomen to the scrotum and is present in about 1% of 1-year-old male infants.

(Ref: Robbins/10th/967; Harsh Mohan/7th/691)

In 70% of cases, the undescended testis lies in the **inguinal ring**, in 25% in the **abdomen** and, in the remaining 5%, it may be present at other sites along its descent from intra-abdominal location to the scrotal sac.

Morphology:

***Gross*:**
- Cryptorchidism is usually unilateral, being bilateral in 25% of patients.
- Cryptorchid testes are small and firm.

***Histologic*:** The histologic changes in the malpositioned testis begin as early as 2 years of age. They are characterized by-
- Thickening of the basement membrane of the spermatic tubules
- Subsequent loss of spermatogonia leaves the tubules with only Sertoli cells
- Increase in interstitial stroma
- Leydig cells are relatively prominent

- Progressive tubular atrophy.

Complication:

1. Sterility
2. Inguinal hernia (in about 10-20% of cases)
3. Development of testicular cancer

Treatment: Surgical correction (orchiopexy).

(Ref: Robbins/10th/966)

Nice to Know:

Causes of testicular atrophy: Testicular atrophy may be caused by one of several conditions, including-

- Progressive atherosclerotic narrowing of the blood supply in old age
- End-stage inflammatory orchitis
- Cryptorchidism
- Hypopituitarism
- Generalized malnutrition or cachexia
- Irradiation
- Prolonged administration of antiandrogens (e.g. for treatment of carcinoma of the prostate)
- Cirrhosis
- Primary failure of genetic origin, such as in klinefelter syndrome
- Exhaustion atrophy (which may follow persistent stimulation by high levels of follicle-stimulating pituitary hormone).

(Ref: Robbins/10th/967)

Q. Give the morphology of seminoma. (DU-22Nv,09Ju, CMU-21/19Nv,15Ju,06, SUST-21/19Nv,11Ju/Ja,08Ja S, RU-15Ju)
Q. Write down the gross and microscopic findings of seminoma. (CMU-22Nv)
Q. Give the morphology of seminoma testis. (CU-17M)
Q. Write down the morphologic features of a typical seminoma. (SU-20M,16/09Ja, RU-07Ja)
Q. Give the histopathology of seminoma. (RMU-22M,09Ja)
Q. Write briefly about seminoma. (RU-20/17Ja)
Q. Short note: Seminoma. (DU-12/11Ja, SMU-23M,22Nv, CMU-22M,16Ja,10Ju, RU-18Nv,11/10Ja)
Ans.

Seminoma: Seminoma is a **malignant germ cell tumour** of testis.

Characteristics of seminoma:

- It is the ***most common testicular germ cell tumor*** (50%)
- Analogous to ***ovarian dysgerminoma***
- Peak incidence is in the ***fourth decade***
- Almost ***never occur in infants***
- Presenting features include ***painless enlargement*** of the testis
- Sometimes this tumor is associated with increased serum ***human chorionic gonadotropin (hCG)***
- They are very ***radiosensitive*** and can often be ***cured.***

Types of seminoma:

1. Classic or typical seminoma
2. Spermatocytic seminoma
3. Anaplastic seminoma

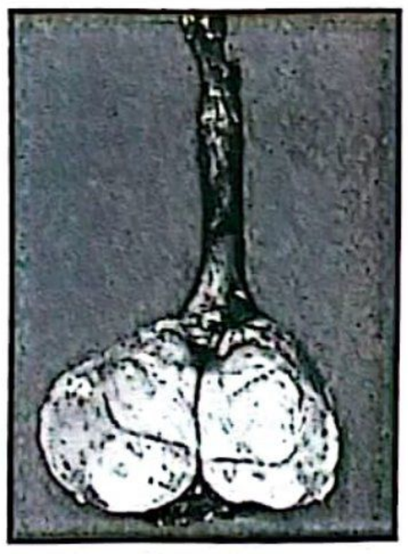


Fig: Seminoma.

Pathology / morphology of seminoma:

Macroscopic:

- Seminomas produce **bulky masses**, sometimes **10 times the size of the normal testis.**
- The **typical seminoma** has a **homogeneous, gray-white, lobulated cut surface,** usually **devoid of hemorrhage or necrosis.**
- Generally the **tunica albuginea is not penetrated,** but occasionally **extension to the epididymis, spermatic cord,** or **scrotal sac** occurs.

Microscopic:

- **Seets of uniform cells** divided into **poorly demarcated lobules** by **delicate fibrous septa** containing a **lymphocytic infiltrate.**
- In some tumors, **ill-defined granulomas** also are present.
- The **classic seminoma cell** is **round to polyhedral** and has a **distinct cell membrane; clear or watery-appearing cytoplasm;** and a **large, central nucleus** with **one or two prominent nucleoli.**
- The cytoplasm contains varying amounts of glycogen.

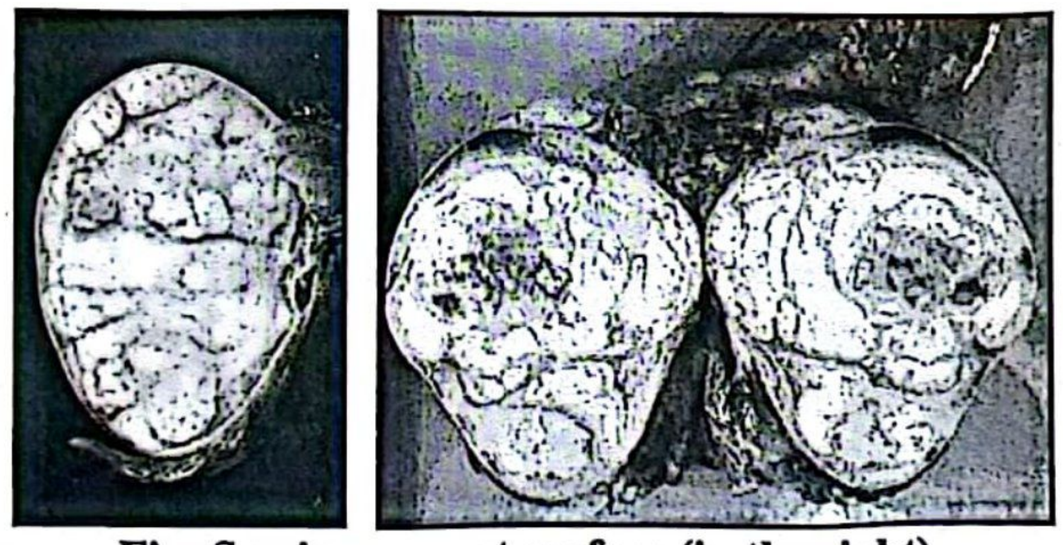


Fig: Seminoma; cut surface (in the right).

(Ref: Robbins/10th/970; BRS Pathology/5th/289)

(***N.B*:** An identical tumor of seminoma arises in the **ovary,** where it is called ***dysgerminoma***, and in the **central nervous system,** usually in midline structures such as the **pineal gland,** where it is referred to as ***germinoma***.)

(Ref: Robbins/10th/970)

Q. Write down the prognosis of a typical seminoma. (SUST-21Nv)

Ans.

Prognosis of a typical seminoma: The prognosis of classic seminoma is better than other germ cell tumours. The tumour is highly radiosensitive and chemosensitive and most patients are cured by orchiectomy with or without chemotherapy or radiotherapy.

(Ref: Robbins/10th/973; Harsh Mohan/7th/715)

Q. Short note: Choriocarcinoma.

Ans.

Choriocarcinoma: Choriocarcinoma is a **highly malignant type of GCT** that can occur as an element of other germ cell tumors.

Characteristics:

a. This tumor is analogous to **choriocarcinoma of the ovary**
b. Incidence peaks in the **second to third decade**
c. Histologic characteristics include cells that resemble placental **syncytiotrophoblasts** and **cytotrophoblasts**
d. This tumor causes an increase in **serum hCG**
e. Highly **chemosensitive.**

Morphology:

***Macroscopic*:**

- Often they cause no testicular enlargement and are detected only as a small palpable nodule.
- Typically, these tumous are small, rarely larger than 5 cm in diameter.
- Haemorrhage and necrosis are extremely common.

***Microscopic*:**

- The tumor is composed of two intimately juxtaposed cell types, **syncytiotrophoblasts** and **cytotrophoblasts.**
- **Syncytiotrophoblasts** are large multinucleated cells with abundant eosinophilic vacuolated cytoplasm containing hCG.
- **Cytotrophoblasts** are more regular and tend to be polygonal, with distinct borders and clear cytoplasm; they grow in cords or sheets and have a single, fairly uniform nucleus.

(Ref: Robbins/10th/972; BRS Pathology/5th/291)

Q. Define teratoma. (RMU-21Nv,15Ja, CU-17M)
Q. Enumerate the morphology of teratoma. (CMU-21M, SU-20M)
Q. Write the morphological features of teratoma of testis. (CU-20Nv)
Q. Write down the morphology of mature teratoma. (CMU-21Nv)
Q. Short note: Teratoma. (DU-17Nv,16/15/14Ja, RU-20Nv,19M,17Ju/M,16Ja,10Ju)
Ans.

Teratoma: Teratoma refers to GCTs having various cellular or organoid components reminiscent of the normal derivatives of **more than one germ layer.**

They may occur at **any age from infancy to adulthood.**

Malignant potential: It is most ***frequently malignant.***

Classification: It can be classified as one of three subtypes:

(1) **Mature teratoma:** This teratoma is **almost always malignant** (whereas the corresponding ovarian tumor is almost always benign)
(2) **Immature teratoma:** Primitive neural elements are often present, and behavior is malignant.
(3) **Teratoma with malignant transformation:** This teratoma contains malignant tissue, such as squamous cell carcinoma.

Morphology:

Gross:

- Teratomas are usually **large** (5-10 cm in diameter).
- Gross appearance is heterogenous with **solid,** sometimes **cartilaginous,** and **cystic areas.**
- **Haemorrhage** and **necrosis** usually indicate admixture with embryonal carcinoma, choriocarcinoma or both.

Microscopic:

- Teratomas are composed of **collections of differentiated cells** or **organoid structures** (such as neural tissue, muscle bundles, islands of cartilage, squamous epithelium lining epidermal-like surfaces with or without skin adnexal structures, structures reminiscent of thyroid gland, bronchial epithelium, and bits of intestinal wall or brain substances) **embedded in a fibrous or myxoid stroma**.
- Elements may be ***mature*** (resembling various adult tissues) or ***immature*** (sharing histologic features with fetal or embryonic tissue).
- **Teratoma with somatic-type malignant transformation:** There may be a focus of squamous cell carcinoma, mucin-secreting adenocarcinoma, sarcoma, or other cancers.

(Ref: Robbins/10th/973; BRS Pathology/5th/290)

Q. Write the differences between seminoma and non-seminomatous germ cell tumor. (DU-19M, BUP-21Nv/M)

Q. How does seminoma differ from non-seminomatous tumor in their behavior? (DU-17/15Ja,13/12Ju)

Q. Mention 3 important differences between seminoma and non-seminomatous germ cell tumors. (DU-08Ja)

Q. Compare and contrast seminomatous and non-seminomatous germ cell tumors.

Ans.

Differences between seminomatous and non-seminomatous germ cell tumors: ***(Important for VIVA)***

Traits	Seminoma	Non-seminomatous germ cell tumor
1. Size of primary tumour	Larger	Smaller
2. Composition	Cells that resemble primordial germ cells or early gonocytes	Undifferentiated cells that resemble embryonic stem cells
3. Occurrence in children	Almost never occur	Occurs e.g. yolk sac tumour, teratoma
4. Clinical stage	Tends to remain localized to the testis for a long time; hence approximately 70% present in clinical stage I	Approximately 60% of patients with NSGCT present with advanced clinical stage (stage II & III)
5. Metastasis	Generally to regional lymph nodes	Haematogenous spread early in the course of dissemination
6. Radiosensitivity	Extremely radiosensitive	Radioresistant
7. Tumour markers	hCG (generally low levels)	hCG, AFP, or both (high levels)
8. Prognosis	Biologically less aggressive and better prognosis	Biologically more aggressive and poorer prognosis

(Ref: Robbins/9th/976-978; Harsh Mohan/7th/695)

Q. Mention the mode of spread of testicular tumor.

Ans.

Mode of spread of testicular tumor: Testicular tumours may spread by both ***lymphatic*** and ***haematogenous*** routes:

1. **Lymphatic spread:** It is common to all forms. In general, retroperitoneal para-aortic nodes are the first to be involved. Subsequent spread may occur to mediastinal and supraclavicular nodes.
2. **Haematogenous spread:** Primarily to the lungs, but liver, brain, and bones may also be involved.

Metastases from seminomas typically involve lymph nodes. Hematogenous spread occurs later in the course of dissemination. Nonseminomatous GCTs tend to metastasize earlier and more frequently via a hematogenous route.

(Ref: Robbins/10th/973; Harsh Mohan/7th/697)

Q. A man of 30 years presented with painless testicular swelling. What is your provisional diagnosis? How you will confirm it? (DU-10Ju)
Q. How will you investigate a case of testicular mass lesions in the laboratory? (DU-21Oct/M)
Ans.
Provisional diagnosis: Testicular tumor (most probably teratoma or seminoma).

Confirmatory laboratory diagnosis:

A. Histopathology:
a. Radical inguinal orchiectomy or biopsy followed by histopathology
b. Fine Needle Aspiration Cytology (FNAC)

B. New techniques:
a. Immunhistochemistry (IHC)
b. Molecular diagnosis
c. Flow cytometry
d. Tumour markers
- α-fetoprotein (AFP)
- Human chorionic gonadotropin (HCG)
- Lactate dehydrogenase (LDH).

(Ref: Robbins/8th/323-327,992; Prof. Khaleque/61,62; Harsh Mohan/7th/696)

Q. What are the testicular tumour markers? (DU-12Ju) **Mention the importance of these markers.**
Q. Name the tumour markers for testicular tumour and their uses. (DU-13Ju)
Ans.

Testicular tumour markers: ***(Very Important for VIVA)***
1. α-fetoprotein (AFP)
2. Human chorionic gonadotropin (HCG)
3. Lactate dehydrogenase (LDH).

Importance of testicular tumour markers: Testicular tumour markers are widely used in the-
- Initial evaluation of testicular masses
- Staging of testicular germ cell tumors
- In assessing tumor burden
- Monitoring the response to therapy (follow-up).

(Ref: Robbins/10th/973; Harsh Mohan/7th/697)

Q. A male of 20 years suddenly noticed painless testicular swelling. What are the tumour markers that should be advised if testicular tumour is suspected? Name the tumours associated with increased beta HCG. (DU-14Ja)
Ans.
Testicular tumour markers:
1. α-fetoprotein (AFP)
2. Human chorionic gonadotropin (HCG)
3. Lactate dehydrogenase (LDH).

Tumours associated with increased β-HCG:
1. Pure seminoma
2. Embryonal carcinoma
3. Choriocarcinoma.

Nice to Know:

Tumours associated with increased AFP:

- *Yolk sac tumor*
- *Embryonal carcinoma.*

Q. A male of 25 years suddenly developed painless left testicular swelling. Name the tumour markers that can help in diagnosis. How can you confirm the diagnosis? (DU-16Ja)

Ans.

Tumour markers that can help in diagnosis in case of painless testicular swelling:

- α-fetoprotein (AFP)
- Human chorionic gonadotropin (HCG)
- Lactate dehydrogenase (LDH)

Confirmatory laboratory diagnosis: *Please write from above.*

Q. A male of 22 years has developed sudden severe pain in the testis. What is your probable diagnosis?

Ans.

Probable diagnosis: Testicular torsion.

Prostate

Q. Enumerate the diseases of prostate. (BUP-21Nv/M)

Q. Name three tumours of prostate. What is the most common?

Ans.

Diseases of the prostate:

a. **Inflammations:**
   - Acute and chronic bacterial prostitis
   - Chronic abacterial prostitis
   - Granulomatous prostitis

b. **Benign enlargement:** Benign prostatic hyperplasia (BPH) or nodular hyperplasia

c. **Tumours:**

   ***Primary tumors*:**
   - Adenocarcinoma of the prostate (most common)
   - Miscellaneous tomours and tumour-like conditions
     - Ductal adenocarconoma
     - Small cell carcinoma of prostate

   ***Secondary tumors*:**
   - Urothelial cancer.

(Ref: Robbins/10th/953,975-982)

Q. Give the pathology / morphology of benign hyperplasia of prostate. (RMU-23M, CU-06S)

Q. Give the microscopic features of nodular hyperplasia of prostate. (RU-12Ja)

Q. Short note: Nodular hyperplasia of prostate. (RU-20Nv, CU-20/16Ju)

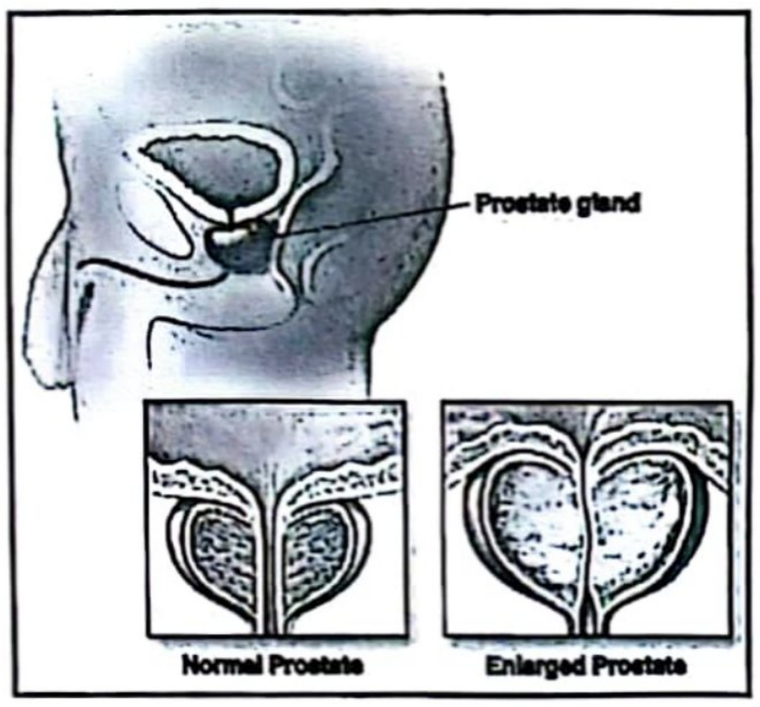
Q. Short note: Benign prostatic hyperplasia. (DU-04M)

Ans.

Benign prostatic hyperplasia: BPH (also referred to as nodular hyperplasia) is the **most common benign prostatic disease** in men **older than age 50 years.**

It results from nodular hyperplasia of prostatic stromal and epithelial cells and often leads to urinary obstruction. It is characterized by the formation of large, fairly discrete nodules in the periurethral region of the prostate, which, when sufficiently large, compress and narrow the urethral canal to cause partial, or sometimes virtually complete, obstruction of the urethra.

It is not a premalignant lesion.



Age of incidence: Over 50 years, most often between 60 & 70.

Morphology:

***Gross*:**

- Prostate is enlarged, weight become 3 to 5 times normal (60 to 100 gm).
- Nodules in lateral lobe may compress urethra to a slit-like orifice.
- Cross section shows hyperplastic nodules of various size, colour and consistency.
- Nodules that contain mostly glands are yellow-pink and soft and exude a milky white prostatic fluid.
- Nodules composed primarily of fibromuscular stroma are pale gray and firm.
- There is no true capsule.

***Microscopic*:**

- Individual nodules contain small to large to cystically dilated glands that are separated by bland spindle-shaped stromal cells.
- The glands are lined by two layers of cells, an inner columnar secretory cell layer and an outer layer of cuboidal or flattened basal epithelium, and infolding of the glands may produce a papillary architecture.
- In markedly enlarged glands, compromise of the vascular supply may produce prostatic infarcts, which may have adjacent areas of squamous metaplasia.

(Ref: Robbins/10th/976)

Fig: Well-defined nodules of BPH compress the urethra into a slitlike lumen.

Q. Give the pathogenesis of benign prostatic hyperplasia.

Ans.

Pathogenesis of benign prostatic hyperplasia: The main androgen in the prostate is **dihydrotestosterone (DHT)**, which is the ultimate mediator of prostatic growth. It is **synthesized in the prostate from testosterone** through the action of **type 2** ***5α-reductase***.

DHT binds to and **activates androgen receptors (ARs)** found in both stromal and epithelial prostate cells. Binding of DHT **stimulates ARs** to translocate from the cytoplasm to the nucleus and **activate the transcription of androgen-dependent genes,** which encode several **growth factors** and **their receptors.**

Although the ultimate cause of BPH is unknown, it is believed that DHT-induced growth factors act by increasing the proliferation of stromal cells and decreasing the death of epithelial cells.

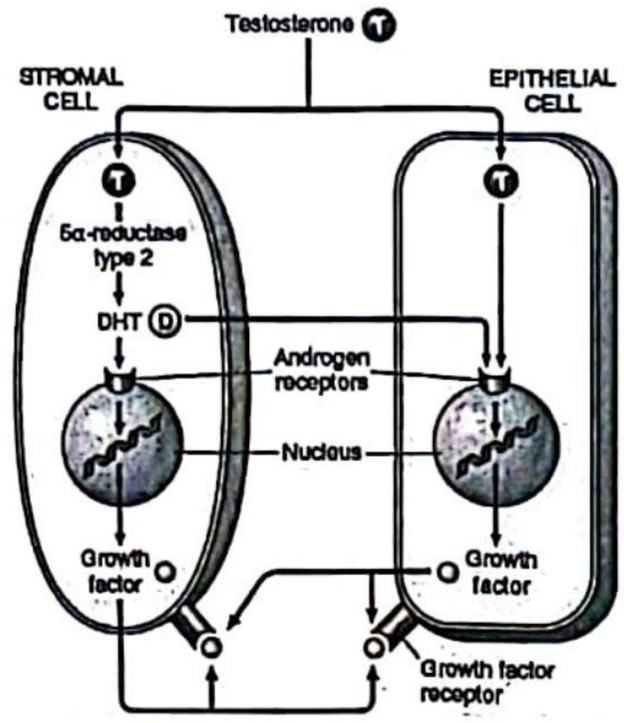


Fig: Pathogenesis of benign prostatic hyperplasia.

(Ref: Robbins/10th/976)

Q. Mention the effects of nodular hyperplasia of prostate.

Ans.

Effects of nodular hyperplasia of prostate:

- Prostatic enlargement and stromal smooth muscle–mediated contraction causes ***urinary obstruction***
- Increased resistance to urinary outflow leads to bladder hypertrophy and distention, accompanied by ***urine retention.***
- The inability to empty the bladder completely creates a reservoir of residual urine that is a common ***source of infection.***

(Ref: Robbins/10th/977)

Q. Mention the clinical features of nodular hyperplasia of prostate.

Ans.

Clinical features of nodular hyperplasia of prostate:

- Increased urinary frequency
- Nocturia
- Difficulty in starting and stopping the stream of urine
- Overflow dribbling
- Dysuria (painful micturition)
- Increased risk of developing bacterial infections of the bladder and kidney
- Sudden acute urinary retention (that requires emergency catheterization for relief).

(Ref: Robbins/10th/977)

Q. Give the difference between benign and malignant prostatic hyperplasia.

Ans.

Difference between benign and malignant prostatic hyperplasia:

1. Benign glands contain basal cells that are absent in cancer.
2. Prostatic cancers have extensive bony metastases, whereas benign enlargements have not.
3. Neoplastic glands are typically smaller than benign glands.
4. In contrast to benign glands, prostate cancer glands are more crowded, characteristically lacking branching and papillary infolding.
5. Serum levels of PSA are elevated to a lesser extent in benign nodular hyperplasia, as compared to cancer.

Traits	Benign prostatic hyperplasia	Malignant prostatic hyperplasia
1. Basal cells	Present	Absent
2. Bony metastasis	No	Yes
3. Size of the gland	Larger	Smaller
4. Architecture	Normal with branching and papillae	More crowded, characteristically lacking branching and papillary infolding
5. Serum PSA level	Elevated to a lesser extent	Elevated to a greater extent

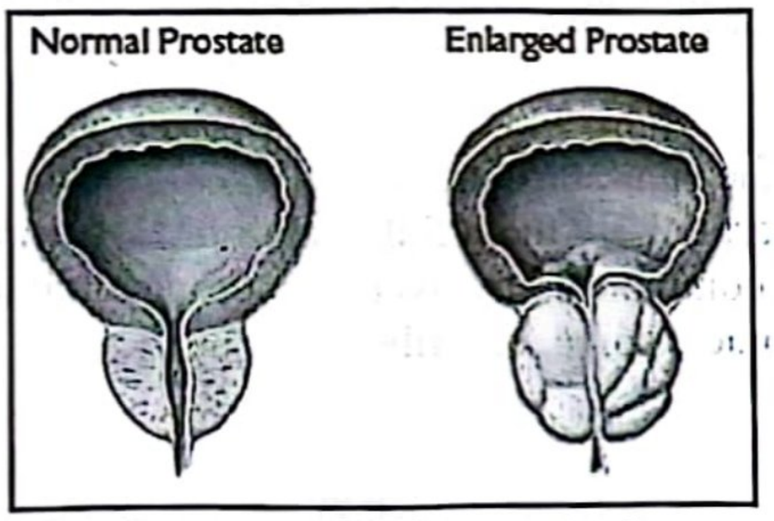


Fig: Benign prostatic hyperplasia.

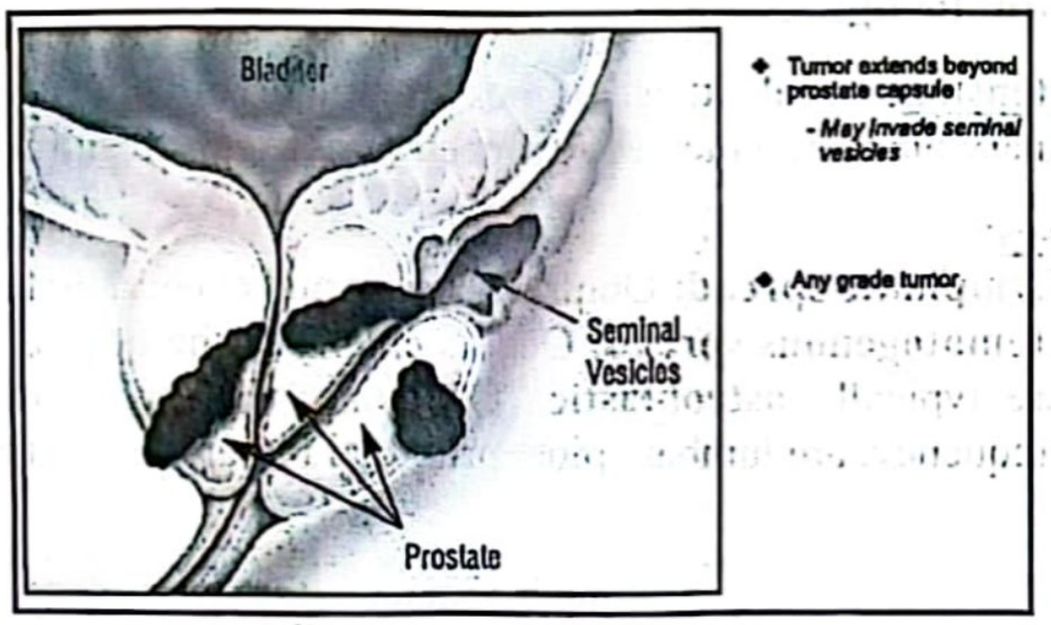


Fig: Malignant prostatic hyperplasia.

(Ref: Robbins/10th/976-982)

Q. Describe the morphological features of most common malignant tumours of prostate. (BUP-21Nv/M)

Q. Short note: Prostatic carcinoma. (CU-14Ja)

Ans.

Prostatic carcinoma:

***Primary tumors*:**

- Adenocarcinoma of the prostate (most common)
- Miscellaneous tomours and tumour-like conditions
  - Ductal adenocarconoma
  - Small cell carcinoma of prostate

***Secondary tumors*:**

- Urothelial cancer.

Prostate cancer is the **second cause of cancer-related death in men,** surpassed only by lung cancer.

Incidence: Men over age 50.

Etiology:

1. Age
2. Race
3. Family history
4. Hormone levels (e.g. androgen)
5. Environmental influence
6. Precursor lesions {prostatic intraepithelial neoplasia (PIN)}.

Morphology:

Gross:

- In approximately 70% of cases, carcinoma of the prostate arises in the **peripheral zone** of the gland
- On cross-section of the prostate the neoplastic tissue is **gritty and firm.**

Microscopic:

- Most *adenocarcinomas* consist of glands arranged in well-defined, easily recognized patterns.

- The glands are typically smaller than benign glands and are lined by a **single uniform layer of cuboidal** or **low columnar epithelium.**
- In contrast to benign glands, malignant glands have **tightly packed cells** and characteristically lack branching and papillary infoldings.
- The **outer basal cell layer** typical of benign glands is **absent.**
- The **cytoplasm** of the tumor cells ranges from **pale-clear to a distinctive amphophilic appearance.**
- **Nuclei** are enlarged and often contain **one or more large nucleoli.**
- There is some **variation in nuclear size and shape,** but in general **pleomorphism is not marked.**
- **Mitotic figures** are **uncommon.**

Local extension: Local extension most commonly involves periprostatic tissue, seminal vesicles, and the base of the urinary bladder, which in advanced disease may result in ureteral obstruction.

Metastases:

- **Lymphatic spread:** Obturator nodes and eventually to the para-aortic nodes.
- **Hematogenous spread:** Occurs chiefly to the **bones,** particularly the **axial skeleton.** Bony metastases are typically **osteoblastic.** The bones that are most commonly involved, in descending order of frequency, are lumbar spine, proximal femur, pelvis, thoracic spine, and ribs.

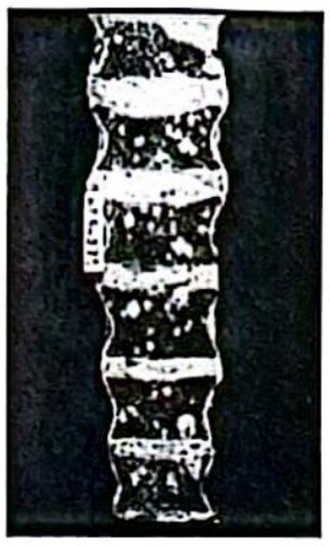


Fig: Metastatic osteoblastic prostatic carcinoma within vertebral bodies.

Clinical course:

- **Localized prostate cancer** is **asymptomatic,** and is usually discovered by the detection of a suspicious nodule on rectal examination or elevated serum PSA level.
- Patients with clinically **advanced prostatic cancer** may present with **symptoms** of **urinary obstruction,** such as difficulty in starting or stopping the stream, dysuria, frequency, or hematuria.
- Some patient pesent with **back pain** caused by **vertebral metastases** and diagnosed by **radionuclide bone scanning.**

Investigations:

- Digital rectal examination (DRE)
- Trans-rectal ultrasound
- Trans-rectal ultraso-guided needle biopsy
- Measurement of serum PSA levels.

Treatment:

1. Surgery (radical prostatectomy)
2. Radiation therapy
3. Androgen deprivation therapy
   - Orchiectomy
   - LHRH agonists.

(Ref: Robbins/10th/978-982)

Nice to Know:

Grade and stage are the most important prognostic factors in prostate cancer. Grading is performed using the ***Gleason system.***

(Ref: Robbins/10th/980)

Q. State the clinical importance / significance of PSA estimation. (DU-10Ja, CU-18Nv)
Q. What is the normal value of PSA? What are the causes of increased PSA?
Q. Describe the value of PSA in prostate cancer. (CU-17M)
Q. Short note: Prostate-specific antigen (PSA). (CU-18M)
Ans.
PSA: Prostate-specific antigen (PSA) is a product of prostatic epithelium and is normally secreted in the semen. It is an androgen-regulated serine protease whose function is to cleave and liquefy the seminal coagulum formed after ejaculation.

In normal men, only minute amounts of PSA circulate in the serum.

Normal value of PSA: 4 ng/ ml.

Causes of increased PSA: PSA is organ specific but not cancer specific. Serum levels of PSA are elevated in-

- Carcinoma of prostate
- Benign prostatic hyperplasia (BPH)
- Prostatis
- Prostate gland infarction
- Instrumentation of prostate
- Ejaculation.

Clinical importance of PSA:

1. Measurement of PSA is the most important test used in the diagnosis and management of prostate cancer.
2. 20-40% of patients with a serum PSA > 4.0 ng/ml will have prostate cancer on biopsy.
3. High levels of serum PSA (> 100 ng/ml) almost always indicate distant bone metastases.
4. PSA is most useful for monitoring response to treatment and disease progression.
5. It is also a tumour marker of some breast cancers.

(Ref: Robbins/10th/981; Davidson's/23rd/439,1322,1324)

Q. A male aged 70 years came with the complaints of progressively increasing difficulty in micturition, urgency and frequency. Per rectal examination revealed palpable prostatic gland. What is the likely diagnosis? Mention the important diagnostic work up for his illness. (DU-18M)
Ans.
Likely diagnosis: Benign prostatic hyperplasia (BPH) or nodular hyperplasia of prostate.

Diagnostic work up:

1. Urine examination:
   - Routine – RBC, glucose, protein, pus cell
   - C/S – infection
   - **Cytology** – if suspicious to exclude malignancy
2. Blood examination:
   - CBC
   - Urea, creatinine, electrolyte
   - Blood sugar
   - **PSA** – to exclude carcinoma prostate
3. USG of whole abdomen
4. Uroflowmetry
5. Urodynamic study
6. IVU *(usually not required unless haematuria)*
7. Cystourethroscopy
8. Transrectal ultrasound scanning
9. **FNAC** in suspected cases of carcinoma prostate.

CHAPTER 10

FEMALE GENITAL SYSTEM

Diseases of female genital tract:

1. **Infections:**
   - **a. Infections of the lower genital tract**
     - *Herpes simplex* virus
     - Other lower female genital tract infections
   - **b. Infections involving the lower and upper genital tract**
     - Pelvic Inflammatory Disease (PID)
2. **Vulva:**
   - **a. Bartholin cyst** (cystic dilatation of the Bartholin gland)
   - **b. Non-neoplastic epithelial disorders**
     - Lichen sclerosus
     - Squamous cell hyperplasia
   - **c. Benign exophytic lesions**
     - Condyloma acuminatum
   - **d. Squamous neoplastic lesions**
     - Vulvar intraepithelial neoplasia and vulvar
     - Carcinoma
   - **e. Glandular neoplastic lesions**
     - Papillary hidradenoma
     - Extramammary paget disease
3. **Vagina:**
   - **a. Congenital anomalies:**
     - Atresia and total absence
     - Septate, or double, vagina

b. Neoplasms:

i. Benign:
- Stromal tumors (stromal polyps)
- Leiomyomas
- Hemangiomas

ii. Pre-malignant: Vaginal intraepithelial neoplasia.

iii. Malignant:
- ***Primary:***
  - Squamous cell carcinoma
  - Embryonal rhabdomyosarcoma (sarcoma botryoides)
- ***Secondary:*** Carcinoma spreading from the cervix.

4. **Cervix:** *Please see below*
5. **Uterus:** *Please see below.*
6. **Ovaries:** *Please see below.*
7. **Gestational and placental disorders:** *Please see below.*

(Ref: Robbins/10th/985-995)

Nice to Know:

Infections of female genital tract:
- *Candida*, *Trichomonas*, and *Gardnerella* are very common, but are **without serious sequelae.**
- *Neisseria gonorrhoeae* and *Chlamydia* infections, are major causes of **female infertility**
- *Group B Streptococcus* infections are implicated in **preterm deliveries, stillbirths,** and **neonatal infections.**
- *Ureaplasma urealyticum* and *Mycoplasma hominis* species account for some cases of **vaginitis** and **cervicitis** and have been implicated in **chorioamnionitis** and **premature delivery in pregnant patients.**
- Viruses, especially *herpes simplex viruses (HSVs)* and *human papillomaviruses (HPVs)*, account for considerable morbidity; HSVs cause **painful genital ulcerations**, whereas HPVs are involved in the pathogenesis of **cervical, vaginal, and vulvar cancers. Molluscum contagiosum** is a cutaneous or mucosal lesion caused by *poxvirus*.

(Ref: Robbins/10th/986-988)

Sexually transmitted diseases (STDs):
- Trichomoniasis
- Gonorrhea
- Mycoplasma
- Chlamydia
- HSV
- HPV
- Syphilis
- Chancroid
- Granuloma inguinale
- Lymphogranuloma venereum.

(Ref: Robbins/10th/986)

Pelvic Inflammatory Disease (PID)

(Important for VIVA)

Q. What do you mean by pelvic inflammatory disease (PID)? Write down the etiology, pathogenesis and complication of PID. (CU-10Ja)

Ans.

Pelvic inflammatory disease (PID): Pelvic inflammatory disease (PID) is an infection that begins in the vulva or vagina and spreads upward to involve most of the structures in the female genital system, resulting in pelvic pain, adnexal tenderness, fever, and vaginal discharge.

(Ref: Robbins/10th/988)

Etiology:

1. Gonococcus infection (most common cause)
2. Chlamydia infection
3. Staphylococci
4. Streptococci
5. Coliform bacteria
6. *Clostridium perfringens.*

(Ref: Robbins/10th/988)

Pathogenesis:

- **Gonococcal PID:** Inflammatory changes start to appear approximately 2 to 7 days after inoculation. Endocervical mucosa is the most common site of initial involvement. Gonococcal infection may also begin in the Bartholin gland and other vestibular, or periurethral glands. From these sites, the organisms may spread upward to involve the fallopian tubes and tubo-ovarian region.
- **Non-gonococcal PID:** The non-gonococcal bacterial infections that follow induced abortion, dilation and curettage of the uterus, and other surgical procedures are thought to spread upward from the uterus through the lymphatics and venous channels rather than on the mucosal surfaces. Therefore, these infections tend to produce more inflammation within the deeper layers of the organs than gonococcal infections.

Complications:

1. **Acute complications:**
   - Peritonitis
   - Bacteremia (which in turn may result in endocarditis, meningitis, and suppurative arthritis).
2. **Remote complications / chronic sequelae:**
   - Infertility, and tubular obstruction
   - Ectopic pregnancy
   - Pelvic pain
   - Intestinal obstruction (due to adhesions between the small bowel and the pelvic organs).

(Ref: Robbins/10th/989)

Cervix

Q. Mention the diseases of cervix.
Q. Mention the carcinoma of cervix.
Q. What are the pre-malignant lesions of cervix? (SUST-21Nv,17M)

Ans.

Diseases of cervix: ***(Important for VIVA)***

A. Non-neoplastic disorders:

- Erosion

- Cervicitis (acute & chronic)
- Endocervical polyps

B. Pre-malignant and malignant neoplastic disorders:

1. Dysplasia and carcinoma in situ {cervical intra-epithelial neoplasia (CIN)}**:**

- **CIN-I:** Mild dysplasia
- **CIN-II:** Moderate dysplasia
- **CIN-III:** Severe dysplasia (carcinoma in situ)

2. Invasive carcinoma: (Caused by high oncogenic risk HPVs)

a. Primary:

- Squamous cell carcinoma (80%)
- Adenocarcinoma (15%)
- Adenosquamous carcinoma
- Small cell neuroendocrine carcinoma } 5%

b. Secondary from colon, breasts, or other sites.

(Ref: Robbins/10th/995-1000; BRS Pathology/5th/300; DeVita/11th/2090; Lecture SSMC)

Q. What do you mean by CIN? (DU-19M,07Ju, RU-21/20Nv,10Ja, CU-18M) **Mention its type.** (RU-20Nv,19M,10Ja)

Q. Mention the cytologic findings of high grade CIN. (SU-10Ju)

Q. Short note: Cervical intra-epithelial neoplasia (CIN). (DU-08Ja, CU-19Nv,07Ja, RU-20M,18Ja)

Q. Short note: Carcinoma in situ, cervix. (RU-13Ja) ***(Important for VIVA)***

Ans.

Cervical intra-epithelial neoplasia (CIN): CIN is a spectrum of ***precancerous changes*** in cervical epithelium, and is graded on progressively severe degree of changes. It includes ***dysplasia*** and CIS (***carcinoma in situ***).

Characteristics:

1. They represent a continuum of morphologic change with indistinct boundaries.
2. They do not invariably progress to cancer and may spontaneously regress, with the risk of persistence or progression to cancer increasing with the severity of the precancerous change.
3. They are associated with human papillomavirus (HPV), and high-risk HPV (types 16, 18 & above) are found in increasing frequency in high-grade CIN.
4. Progression to invasive carcinoma (when it occurs) may take place in a few months to more than a decade.

Classification: CIN have been classified in a variety of ways-

A. Cervical intra-epithelial neoplasia (CIN) system (depending on the extent of epithelial involvement)**:**

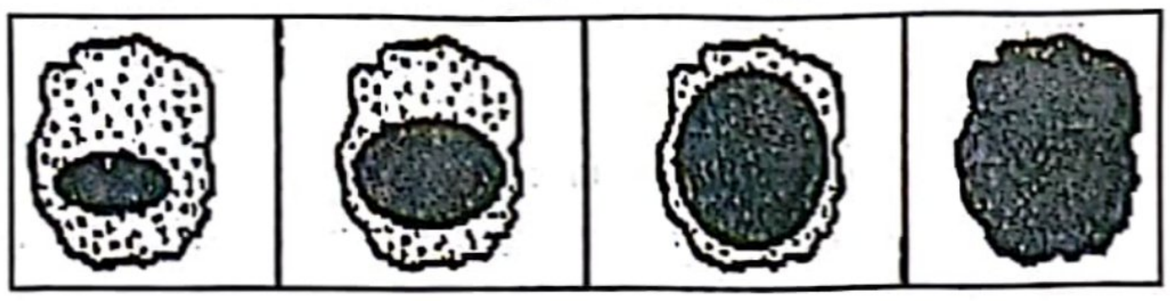
1. CIN-I: Mild dysplasia
2. CIN-II: Moderate dysplasia
3. CIN-III: Severe dysplasia (***carcinoma in situ***).

B. Dysplasia / carcinoma in situ system:

1. Mild dysplasia
2. Severe dysplasia (***carcinoma in situ***)

C. Squamous intra-epithelial lesion (SIL), current classification: The three-tier classification system (CIN) has been recently simplified to a two-tiered system-

1. ***Low grade*** **squamous intra-epithelial lesion (LSIL):** CIN-I (mild dysplasia).
2. ***High grade*** **squamous intra-epithelial lesion (HSIL):** CIN-II & CIN-III (moderate & severe dysplasia, ***carcinoma in situ***).



A B C D

Fig: A = CIN-I; B = CIN-II; C = CIN=III; D = Invasive cancer.

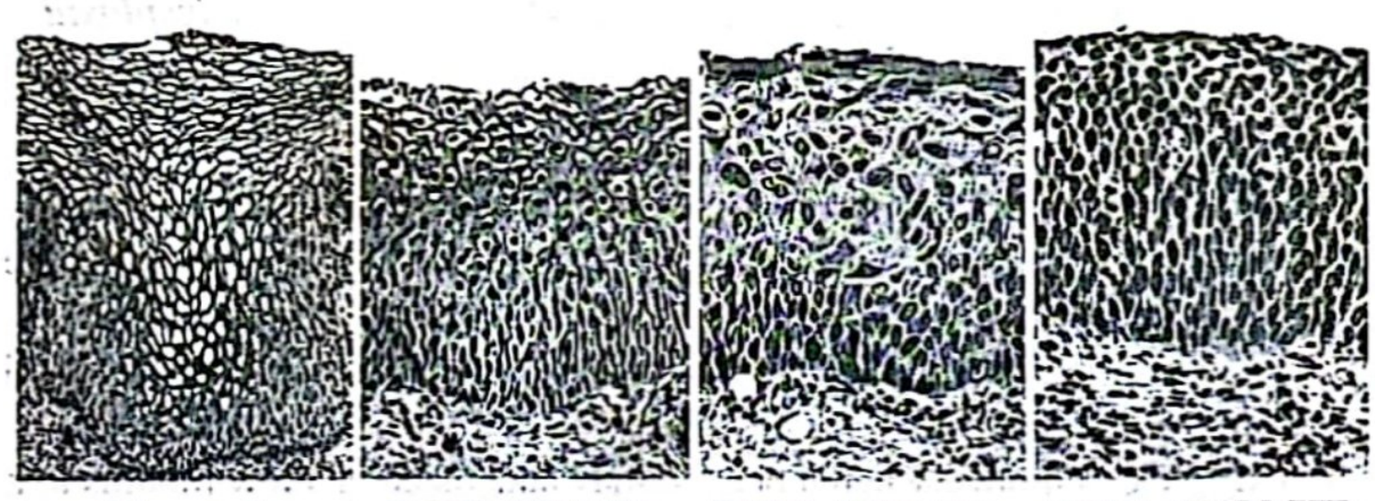
Morphology: Important morphologic features of CIN are-

- Cellular immaturity
- Cellular disorganization
- Nuclear abnormalities
- Increased mitotic activity

1. **Low-grade SIL (CIN-I):**
   - ***Mild dysplasia & atypia.***
   - Lesions involving the ***lower 1/3rd*** of the epithelium.
2. **High-grade SIL (CIN-II & III):**
   a. **CIN-II:**
      - ***Moderate dysplasia & progressive atypia.***
      - Lesions involving the ***lower & middle 3rd*** of the epithelium.

   b. **CIN-III** (carcinoma in situ)**:**
      - ***Severe dysplasia, diffuse atypia & loss of maturation.***
      - Lesions extending through the ***entire thickness*** of the epithelium ***up to the epithelial surface.***

(Ref: Robbins/10th/997; BRS Pathology/5th/301; DeVita/11th/2094)



Normal LSIL (CIN-I) HSIL (CIN-II) HSIL (CIN-III)

Fig: Squamous intra-epithelial lesion (SIL).

Squamous Intraepithelial Lesions (LSIL and HSIL): LSIL does not progress directly to invasive carcinoma, and, in fact, most cases regress spontaneously; only a small percentage progress to HSIL. By contrast to LSIL, HSIL is considered to be at high risk for progression to carcinoma.

LSIL is approximately ten times more common than HSIL. Although the majority of HSILs develop from LSILs, approximately 20% of cases of HSIL develop de novo, independent of any preexisting LSIL.

More than 80% of LSILs and 100% of HSILs are associated with high-risk HPVs, with HPV-16 being the most common HPV type in both lesions.

Progression to invasive carcinoma, when it occurs, on average takes place over several decades.

(Ref: Robbins/10th/997)

Q. Compare and contrast low grade and high grade cervical intra-epithelial neoplasia.

Ans.

Comparison between low grade and high grade cervical squamous intra-epithelial neoplasia: *(For VIVA)*

Traits	Low grade SIL	High grade SIL
1. Dysplasia	Low grade (CIN-I)	Moderate to high grade (CIN-II, CIN-III, carcinoma in situ)
2. Cellular proliferation	Low	High
3. Associated with	Low risk HPV types	High risk HPV types
4. Risk of progression to invasive cancers	Low	High
5. Frequency	More common	Less common
6. Spontaneous regression	Possible	Not possible

(Ref: Robbins/10th/997; DeVita/11th/2094)

Nice to Know:

Staging of cervical cancer: Cervical cancer staging is the assessment of cervical cancer to decide ***how far the disease has progressed.***

Stage 0 (pre-cancerous or non-invasive)**:** Carcinoma in situ (CIN-III, HSIL).

Stage I: Carcinoma confined to the cervix.

- **Ia.** Invasive carcinoma diagnosed only by microscope & depth of invasion not more than 7 mm.
- **Ib.** Clinically visible lesion confined to the cervix or microscopic lesion greater than stage Ia.

Stage II: Carcinoma extends beyond the cervix but not to the pelvic wall or lower third of the vagina.

Stage III: Carcinoma extended onto the pelvic wall & involves the lower third of the vagina.

Stage IV: Carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum. This stage obviously includes those with metastatic dissemination.

{Ref: Robbins/10th/999 (modified); AJCC Cancer Staging Manual/8th/661}

Q. Describe briefly the etiopathogenesis of carcinoma of cervix. (DU-07Ju, CMU-23/18/17M,16Ju,05Ja, SU-14/08/07Ju,05Ja, RU-10Ja)
Q. State the etiologic factors of carcinoma of cervix. (CU-20Nv/M)
Q. Write down the role of HPV in causing cervical cancer. (DU-19M, SU-18M,15Ju)
Q. Nerrate the pathogenesis of carcinoma cervix. (BUP-22Nv, CU-19M, RU-17Ju/M,14/13Ju,11Ja)
Q. Give the pathogenesis of cervical pre-cancer. (RU-16Ja)
Q. Briefly narrate pathogenesis of cervical pre-cancer and cancer. (RU-19M)
Q. Write the risk factors for carcinoma cervix. (RMU-22/19Nv, CMU-21Nv,20Ju,16Ja,13Ju)

Ans.

Etiology / risk factors for carcinoma cervix:

1. Early age at first intercourse
2. Multiple sexual partners
3. Male partner with multiple previous sexual partners
4. Early first pregnancy
5. Multiparity
6. Persistent infection with high risk HPV (types 16, 18 and above)
7. STDs
8. Cigarette smoking
9. Oral contraceptive pill (OCP)
10. Immunosuppression
11. Low socio-economic status.

(Ref: Robbins/10th/998; Manual of Clinical Oncology/7th/322; BRS Pathology/5th/301)

Pathogenesis:

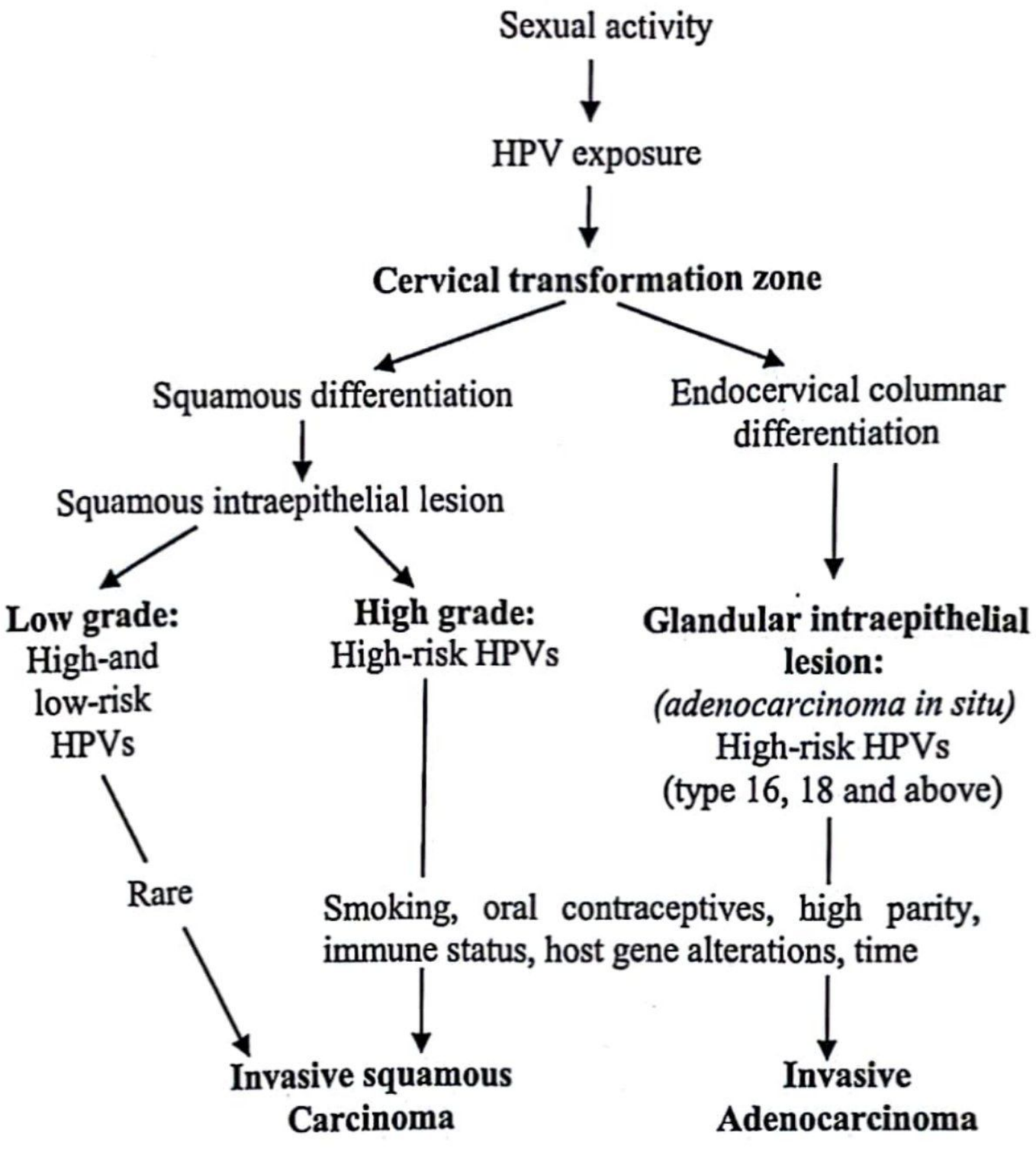

Sexual activity
HPV exposure
Cervical transformation zone
Squamous differentiation
Endocervical columnar differentiation
Squamous intraepithelial lesion
Low grade: High-and low-risk HPVs
High grade: High-risk HPVs
Glandular intraepithelial lesion: (adenocarcinoma in situ) High-risk HPVs (type 16, 18 and above)
Rare
Smoking, oral contraceptives, high parity, immune status, host gene alterations, time
Invasive squamous Carcinoma
Invasive Adenocarcinoma

Fig: Pathogenesis of cervical carcinoma.

(Ref: Robbins/10th/996,998)

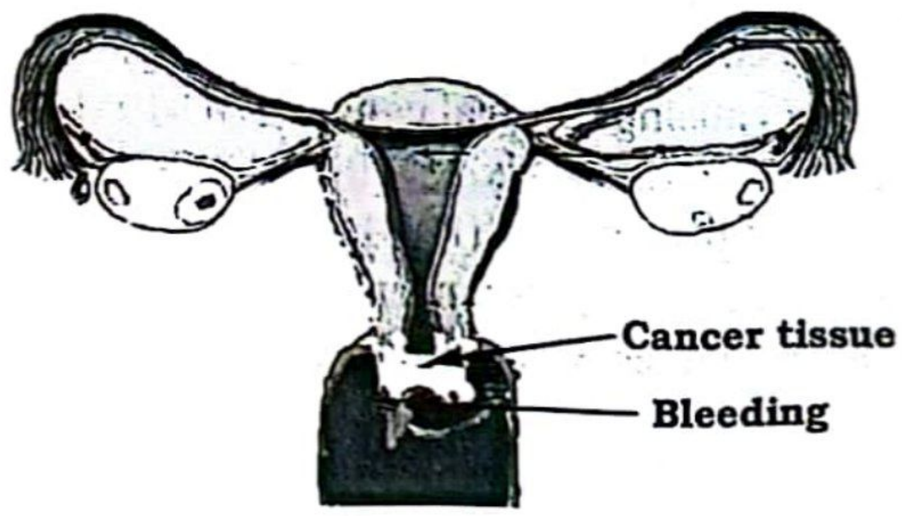


Fig: Carcinoma of cervix.

Nice to Know: *(Very Important for VIVA & MD/MS Residency MCQ)*

Human papilloma virus (HPV): HPV variants are classified as **high-risk** or **low-risk** types based on their propensity to induce carcinogenesis.

- **Low risk types** - 6, 11 and below (causes ***genital warts*** and ***laryngeal papilloma***).
- **High risk types** - 16, 18 (and above, e.g. 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 & 68 etc.) (causes ***invasive cervical carcinoma*** and ***high grade CIN***).

(Ref: Robbins/10th/996)

The duration of the infection is related to HPV type; on average, infections with high oncogenic risk HPVs last longer than infections with low oncogenic risk HPVs, 13 months versus 8 months, respectively. Persistent infection increases the risk of the development of cervical precancer and subsequent invasive carcinoma. All of the **cervical carcinomas** are caused by **high oncogenic risk HPVs (type 16, 18 & above).**

High oncogenic risk HPVs (type 16, 18 & above) are currently considered to be the ***single most important risk factor*** in cervical oncogenesis. High oncogenic risk HPVs (type 16, 18 & above) have also been detected in **vaginal SCC** & in a subset of **vulvar, penile, anal, tonsillar** & other **oropharyngeal carcinomas.**

(Ref: Robbins/10th/996; Lecture SSMC)

High-risk HPV produces **E6 & E7 proteins** which result in increased destruction of **p53** and **Rb,** respectively. ***Loss of these tumour suppressor proteins*** increases the risk for **CIN.**

(Ref: Pathoma/2014/139)

Q. Short note: Transformation zone. (RU-19Nv)

Ans.

Transformation zone: Anatomically, cervix is divided into the **exocervix** (visible on vaginal exam) and **endocervix.**

- Exocervix is lined by **squamous epithelium.**
- Endocervix is lined by **columnar (mucus-secreting) epithelium.**

The point where the squamous and columnar epithelium meets is referred to as the ***squamocolumnar junction.***

With the onset of puberty, the squamocolumnar junction undergoes eversion, causing the columnar epithelium to become visible on the exocervix. The exposed columnar cells, however, eventually undergo **squamous metaplasia,** forming a region called the ***transformation zone,*** where tumors most commonly arise.

So, the area of the cervix where the columnar epithelium abuts the squamous epithelium is termed the "***transformation zone.***"

Or,

The region of the cervix where **squamous metaplasia** occurs is referred to as the "***transformation zone***".

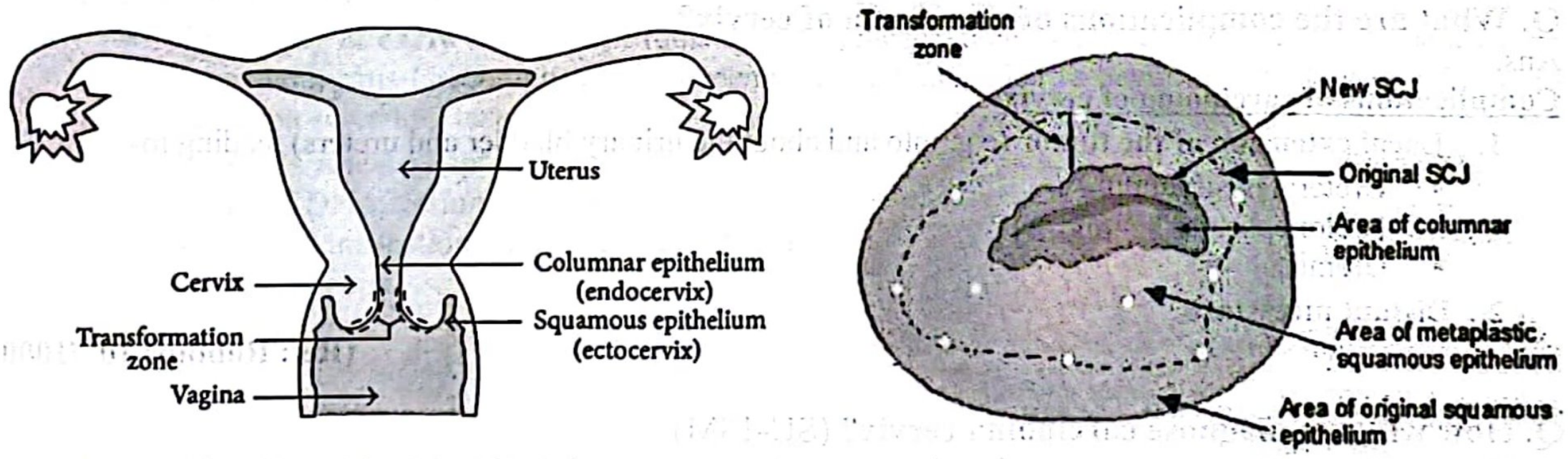


Fig: Cervical transformation zone.

Importance: Most tumors of the cervix are of epithelial origin and are caused by oncogenic strains of HPV. Immature squamous metaplastic epithelial cells in the transformation zone are most susceptible to HPV infection, and as a result this is where cervical precursor lesions and cancers develop.

(Ref: Robbins/10th/995; Pathoma 2011)

Q. Give the morphology of cervical carcinoma.
Q. Give the morphology of cervical squamous cell carcinoma. (CU-07Ja)
Ans.
Cervical carcinoma:

- It is one of the most common neoplasms in women.
- Average age of patients is between 45 and 50 years.
- With the advent of widespread screening (by Pap test), many cervical carcinomas are detected at sub-clinical stage, so death due to this has declined sharply.

Morphology of cervical carcinoma: Invasive cervical carcinoma may manifest as ***fungating*** (exophytic) or ***infiltrative*** masses. On histologic examination-

- **Squamous cell carcinomas:** These are composed of nests and tongues of malignant squamous epithelium, either keratinizing or non-keratinizing, invading the underlying cervical stroma.
- **Adenocarcinomas:** They are characterized by proliferation of glandular epithelium composed of malignant endocervical cells with large, hyperchromatic nuclei and relatively mucin-depleted cytoplasm, resulting in dark appearance of the glands, as compared with the normal endocervical epithelium.
- **Adenosquamous carcinomas:** They are composed of inter-mixed malignant glandular and squamous epithelium.
- **Neuroendocrine carcinomas:** They typically have an appearance similar to small-cell carcinoma of the lung, but differ in being positive for high-risk HPVs.

(Ref: Robbins/10th/998,999)

Q. How cervical carcinoma spread?
Ans.
Spread of cervical carcinoma:

- **Direct spread** by **local extension** into other pelvic structures, including paracervical soft tissue, urinary bladder, ureters (resulting in hydronephrosis), rectum, and vagina. Lymphovascular invasion results in local and distant lymph nodes metastases.
- **Distant (blood-borne) metastasis** to the liver, lungs, bone or bone marrow.

(Ref: Robbins/10th/999; Manual of Clinical Oncology/7th/323)

Q. What are the complications of carcinoma of cervix?
Ans.
Complications of carcinoma of cervix:

1. **Local extension of the tumor** (e.g. into and about the urinary bladder and ureters) leading to-
   - Ureteral obstruction
   - Pyelonephritis
   - Uremia.
2. **Distant metastasis.**

(Ref: Robbins/10th/1000

Q. How will you diagnose carcinoma cervix? (SU-18M)
Q. How will you diagnose a case of early stage of cancer cervix? (SU-15/07Ju,05Ja, CU-05Ja)
Q. How will you proceed to diagnose a case of Ca cervix? (SUST-21Nv,17M)
Q. What are the investigations done to prevent cervical cancer? (CU-17M)
Q. Mention the diagnostic tool of cervical cancer. (DU-19M)
Q. Write the methods of Lab. diagnosis of cervical cancer. (CMU-22M)
Ans.
Diagnostic procedure of carcinoma cervix: (V.V.I. for VIVA)

1. **History** (evaluation of symptoms):
   - Unexplained vaginal bleeding (particularly post-coital bleeding)
   - Foul smelling vaginal discharge
   - Painful coitus(dyspareunia)
   - Pelvic pain
   - Weight loss
   - Obstructive uropathy.

2. **Clinical examination** (signs):
   - Cervix is fixed
   - Hard in consistency
   - Irregular & friable
   - Bleeds on touch.

3. **Investigations** (to confirm the diagnosis):
   - Visual inspection by acetic acid (VIA)
   - HPV DNA testing by PCR
   - Pap's smear
   - Colposcopy and colposcopy-guided biopsy followed by histopathology.

(Ref: Robbins/10th/1000; Manual of Clinical Oncology/7th/324; DeVita/11th/2090)

Q. How carcinoma cervix can be prevented? (BUP-22Nv)
Q. Short note: Cervical cancer screening and prevention.
Ans.

Prevention of cervical cancer: (V.V.I. for VIVA)

1. **Primary prevention:**
   - ***Avoidence of the precipitating and risk factors*** (e.g. early marriage, multiple sex partners, smoking etc.)
   - ***Counseling / health education:*** To reduce high risk sexual behavior & to encourage safe sexual behavior (e.g. use of condom).
   - ***Vaccination:*** Prophylactic HPV vaccine (against HPV types 6, 11, 16, and 18) for all school girls (12-18 years) and women (16-25 years) with dose schedule 0-2-6 months.

2. **Secondary prevention:**
   - **Screening & early detection:** Premalignant / precancercous stages can be detected by some non-invasive means (screening tests). Screening is recommended to begin at age 21 years. The most common screening tests are:
     - Pap's smear / Pap's test
     - HPV DNA testing by PCR
     - Visual inspection with acetic acid (VIA)
     - Colposcopy.

3. **Treatment** (for the pre-malignant lesions).

(Ref: Robbins/10th/1000; DeVita/11th/2090)

(***N.B*: *Screening*** means systematic application of a test in ***asymptomatic person*** to identify ***pre-clinical*** lesions).

Q. What is Pap test? (CU-18M)
Q. How you will collect the Pap smear? (SU-10Ju) **Give importance of Pap smear test.**
Q. Short note: Paps smear / Pap test. (CMU-22Nv,13Ja, RU-19M,17Nv, SU-14Ju/Ja,11Ju)
Ans.

Pap test: Pap tests are **cytologic preparations** of **exfoliated cells** from the cervical **transformation zone** that are stained with the **Papnicolaou method.**

(Ref: Robbins/100th/1000)

Or,

A Pap smear, also called a Pap test, is a ***screening procedure for cervical cancer***. It tests for the presence of **pre-cancerous** or **cancerous cells** on the **cervix**.

Procedure:

1. **Sample (cell) collection:** Using a **spatula** or **cytobrush**, the ***transformation zone*** of the cervix is circumferentially **scraped** for **sample** (cell) **collection**.
2. **Smearing:** Collected **specimen** (cells) is **smeared** on clean **glass slides**.
3. **Fixation:** By **95% alcohol**.
4. **Staining & examination under microscope:** The **stained slide** is then **examined under a microscope** by the **cytotechnologist** (a person specifically trained to identify cytologic abnormalities).

(Ref: Robbins/10th/1001; Manual of Clinical Oncology/7th/323,324)

Schedule for Pap test: In general the **first smear** should be at **21 years of age** or **within 3 years of onset of sexual activity**, and thereafter **every 3 years. After 30 years of age,** women who have had **normal cytology** results and are **negative for HPV** may be **screened every 5 years.** Women who have a **normal cytology** result but **test positive** for **high-risk HPV DNA** should have cervical cytology repeated every **6 to 12 months.**

(Ref: Robbins/10th/1001)

Papanicolaou's grading:

Class I : Normal.
Class II : Inflammatory atypia (infection).
Class III : Mild dysplasia (CIN-I), moderate dysplasia (CIN-II).
Class IV : Severe dysplasia / carcinoma in situ (CIN-III).
Class V : Invasive squamous carcinoma.

(Ref: DeVita/11th/2094)

Importance of Pap test:

1. It is the main screening tool for cervical diseases, especially carcinoma cervix.
2. It is also used to get advice about further investigations like colposcopy.

(***N.B:*** False negative error rate of Pap test is around 10-20%).

(Ref: Manual of Clinical Oncology/7th/323,324)

Q. A female of 55 years presented with an ulcerated growth in cervix, which bleeds on touch. What is your clinical diagnosis? What do you expect in histopathology and name the microbial agent associated with it. (DU-22Nv,21Oct/M,13Ju)

Ans.

Clinical diagnosis: Carcinoma cervix.

Histopathology: *Please write from above.*

Microbial agent associated with carcinoma cervix: Human papilloma virus (HPV) {High oncogenic risk HPVs (type 16, 18 and above)}.

(Ref: Robbins/10th/1001)

Q. A female of 65 years age has presented with per-vaginal bleeding for last 15 days. Oncolposcopic examination cervix shows an ulcerated polypoid lesion, which bleeds on touch. Other investigations like VIA is positive. What is the likely diagnosis? What are the other relevant investigations are carried out in that case? (DU-23Nv)

Q. A female of 45 years old presented with lower abdominal pain, per vaginal bleeding with foul smelling discharge. On examination her cervix shows an ulcerated growth. Give the provisional diagnosis. Mention the investigations needed to confirm the diagnosis. (DU-21Ja,20Nv/M,19Nv)

Q. A cachectic woman of 40 years presents with P/V discharge and contact bleeding for last 3 months. On examination a friable whitish growth is seen which bleeds on touch. What is the probable diagnosis? How will you confirm the diagnosis? (DU-15Ju,11Ja)

Ans.

Provisional diagnosis: Carcinoma of cervix.

Investigations needed to confirm the diagnosis:

- Visual inspection by acetic acid (VIA)
- HPV DNA testing by PCR
- Pap's smear
- Colposcopy and colposcopy-guided biopsy followed by histopathology.

Body of the Uterus & Endometrium

Basics:

- **Endometrium** - Mucosal lining of uterus.
- **Myometrium** - Smooth muscle underlying the endometrium.

Hormone cycle of endometrium:

Proliferative phase	Estrogen driven	Endometrium grows
Secretory phase	Progesterone driven	Endometrium prepares for implantation
Menstrual phase	Due to loss of progesterone	Endometrium falls

(Ref: Pathoma Lecture Notes)

Q. Mention the diseases of uterus.

Q. Classify the tumours of uterus. (RU-19M,16Ja,13Ju)

Ans.

Diseases of uterus:

1. **Functional endometrial disorders** (dysfunctional uterine bleeding)
2. **Inflammatory disorders:**
   - ***Acute endometritis*:** It usually occurs due to retained products of conception (after delivery or miscarriage). Causative agents include group-A hemolytic streptococci, staphylococci, and other bacteria.
   - ***Chronic endometritis*:** It occurs in association with the following disorders:
     - Chronic pelvic inflammatory disease (gonorrhea, chlamydia)
     - Retained gestational tissue (postpartum or post-abortion)
     - Intrauterine contraceptive devices (IUD)
     - Tuberculosis
3. **Endometriosis**
4. **Adenomyosis**

5. **Tumors of uterus:**

A. Endometrium:

a. Benign:
- Endometrial polyp
- Endometrial hyperplasia

b. Malignant:
- Endometrial carcinoma
- Carcinosarcomas (malignant mixed müllerian tumors)
- Adenosarcomas
- Endometrial stromal tumors (stromal sarcoma)

B. Myometrium:

a. Benign: Leiomyoma (fibroids)

b. Malignant: Leiomyosarcoma.

(Ref: Robbins/10th/1001-1015; Pathoma Lecture Notes)

Q. What are the causes of abnormal uterine bleeding? (RMU-23/22/21/19M,17Ju/M,15Ju, SU-10/06Ja)

Q. Short note: Abnormal uterine bleeding. (RU-11Ju)

Ans.

Causes of abnormal uterine bleeding by age group:

Age group	*Causes*
Pre-puberty	Precocious puberty (hypothalamic, pituitary or ovarian origin)
Adolescence	Anovulatory cycle, coagulation disorders
Reproductive age	1. Complications of pregnancy ▪ Abortion ▪ Trophoblastic disease ▪ Ectopic pregnancy 2. Anatomic lesions ▪ Leiomyoma ▪ Adenomyosis ▪ Polyps ▪ Endometrial hyperplasia ▪ Carcinoma 3. ***Dysfunctional uterine bleeding*** ▪ Anovulatory cycle ▪ Ovulatory dysfunctional bleeding (e.g. inadequate luteal phase)
Perimenopausal	1. ***Dysfunctional uterine bleeding*** ▪ Anovulatory cycle ▪ Irregular shedding 2. Anatomic lesions ▪ Carcinoma ▪ Hyperplasia ▪ Polyps
Postmenopausal	1. Endometrial atrophy 2. Anatomic lesions ▪ Carcinoma ▪ Hyperplasia ▪ Polyps

(Ref: Robbins/10th/1003; Harsh Mohan/7th/721)

Q. What is DUB? Mention the causes of DUB according to age. (CU-20Nv, RU-18M, SU-14Ju)
Q. Short note: Dysfunctional uterine bleeding.
Ans.
Dysfunctional uterine bleeding (DUB): This is a clinical term for ***uterine bleeding that lacks an underlying structural abnormality***.

Or,

Dysfunctional uterine bleeding (DUB) may be defined as ***excessive bleeding*** occurring during or between menstrual periods ***without a causative uterine lesion*** such as tumour, polyp, infection, hyperplasia, trauma, blood dyscrasia or pregnancy.

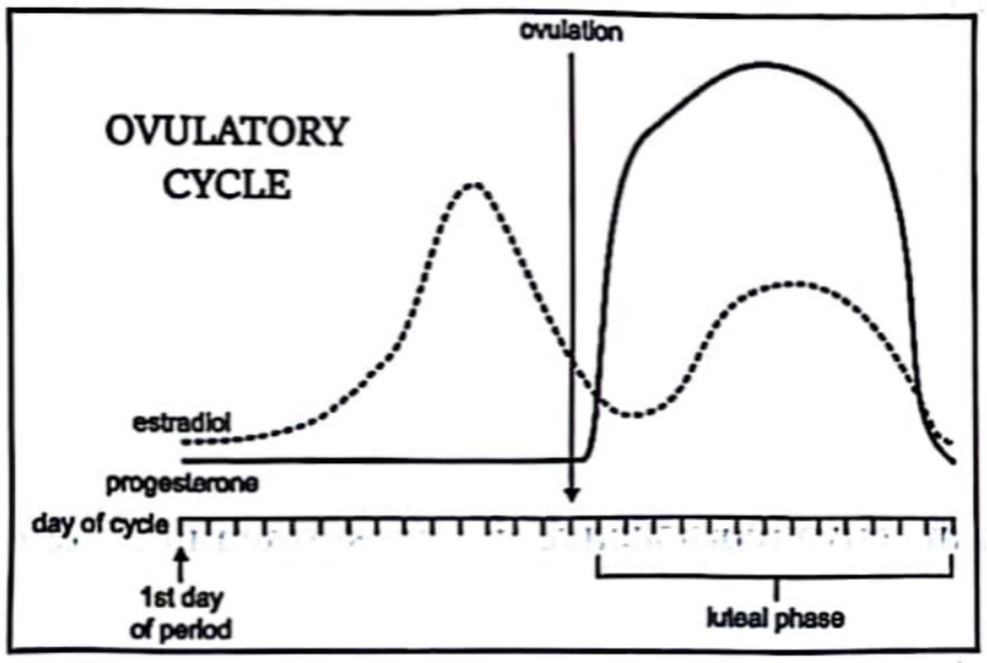
Causes of DUB according to age: *Please write from the table above.*

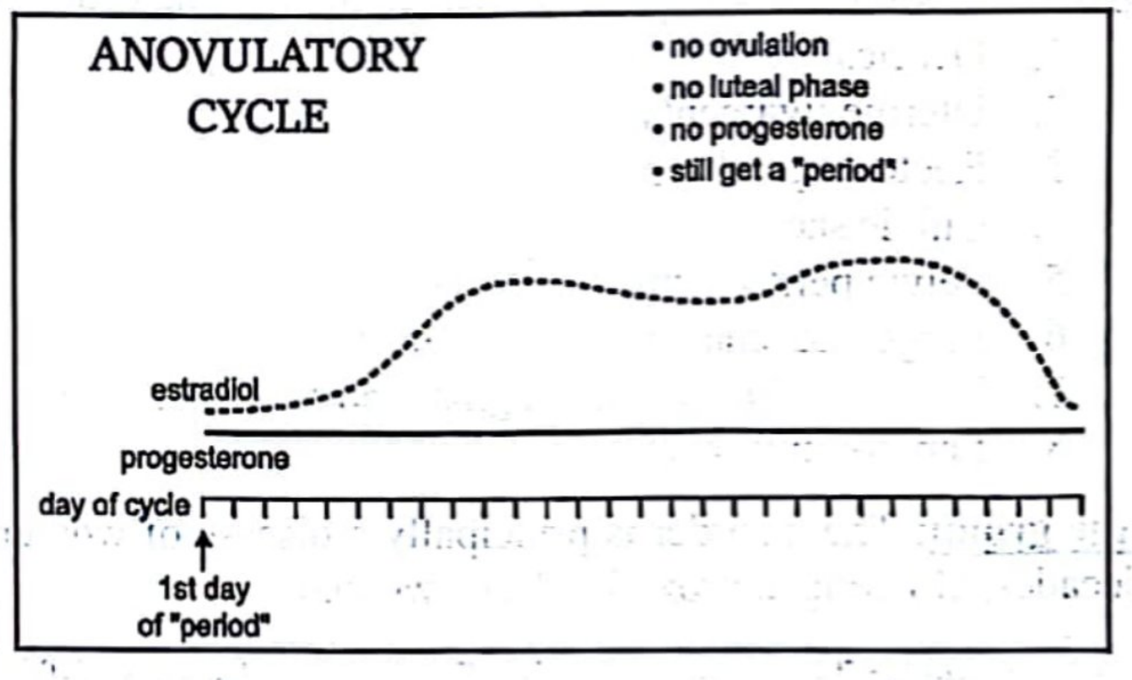
Common causes of DUB:
1. Anovulatory cycle
2. Ovulatory dysfunctional bleeding (inadequate luteal phase)
3. Hormonal contraceptives
4. Irregular sheeding.

(Ref: Robbins/10th/1002; Harsh Mohan/7th/721)

Q. Enumerate the causes of anovulatory cycle. (RU-20M,16/10Ju)
Q. Short note: Anovulatory cycle. (RU-18Nv)
Ans.
Anovulatory cycle: Anovulation or an anovulatory cycle is a menstrual cycle with **no ovulation** (***failure to ovulate***). It is the most frequent cause of dysfunctional uterine bleeding during menarche and menopause.

Failure of ovulation (anovulation) is the result of ***prolonged and excessive oestrogenic stimulation without the development of progestational (luteal) phase***.





Causes of anovulatory cycle: Anovulatory cycles result from hormonal imbalances and are most common at menarche and in the perimenopausal period. Less commonly, anovulation is the result of the following:

1. **Endocrine disorders:**
   - Thyroid disease
   - Adrenal disease
   - Pituitary tumors
2. **Ovarian lesions:** Functioning ovarian tumor (granulosa cell tumors) or polycystic ovaries.
3. **Generalized metabolic disturbances:**
   - Obesity
   - Malnutrition
   - Other chronic systemic diseases.

(Ref: Robbins/10th/1003; Harsh Mohan/7th/721; Pathoma Lecture Notes)

Q. What do you mean by endometriosis? (RMU-22/21/20M,09Ju, CMU-22M,19Nv, BUP-21Nv/M) **Write down the common site of endometriosis.** (CMU-23/22M,15Ja,14Ju, BUP-21Nv/M, RU-20Nv) ***(Important for VIVA)***

Q. Write down the complications of endometriosis. (BUP-21Nv/M)

Q. Short note: Endometriosis. (DU-23M,07/05Ja, RU-19/18Nv,17Nv/Ja,16/15/14/13/12Ja, CU-12Ju, SU-06Ja)

Ans.

Endometriosis: Endometriosis is defined by the presence of **"ectopic" endometrial tissue** ***at a site outside of the uterus.***

The **abnormal tissue** most commonly includes both **endometrial glands** and **stroma,** but may consist only of stroma in some cases.

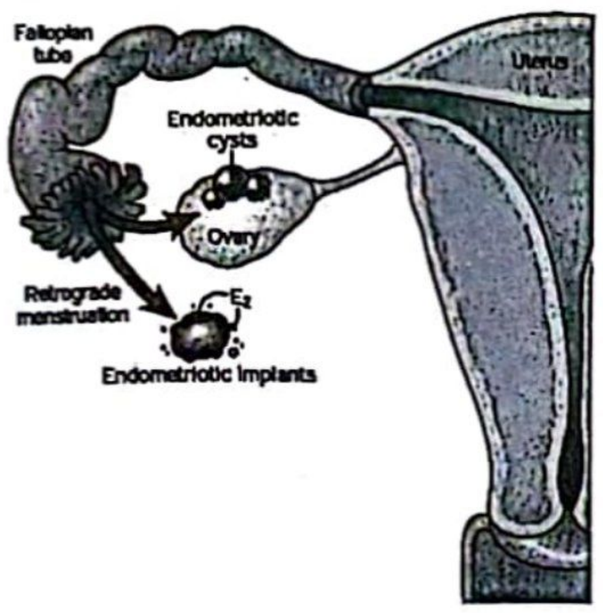


Fig: Endometriosis.

Sites: It occurs in the following sites, in descending order of frequency-

1. Ovaries
2. Uterine ligaments
3. Recto-vaginal septum
4. Cul de sac
5. Pelvic peritoneum
6. Large and small bowel and appendix
7. Mucosa of the cervix, vagina, and fallopian tubes
8. Laparotomy scars.

Age group: The disorder is principally a disease of women in active reproductive life, most often in 3rd & 4th decades, affecting approx. 6-10% of women.

Pathogenesis: The major theories for the development of endometriosis- ***(Important for VIVA)***

1. **Regurgitation theory:** According to this, endometrial tissue is implanted at abnormal locations. Retrograde menstruation through the fallopian tubes occurs regularly even in normal women and could mediate spread of endometrial tissue to the peritoneal cavity.
2. **Benign metastases theory**: According to this, endometrial tissue from the uterus can "spread" to distant sites (e.g., bone, lung, and brain) via blood vessels and lymphatic channels.
3. **Metaplastic theory:** *Metaplastic theory* suggests that ectopic endometrium develops *in situ* from local tissues by metaplasia of the coelomic epithelium (mesothelium of pelvis or abdomen).
4. **Extrauterine stem/progenitor cell theory:** It is a recent idea that proposes that stem/progenitor cells from the bone marrow differentiate into endometrial tissue.

Clinical features:

1. Severe dysmenorrhea *(painful menstruation)*
2. Dyspareunia *(pain with intercourse)*

3. Pelvic pain (due to intrapelvic bleeding and periuterine adhesions)
4. Pain on defecation (due to rectal wall involvement)
5. Dysuria (due to involvement of bladder wall)
6. Menstrual irregularities
7. Infertility *(in 30-40% of women)* - due to involvement of fallopian tube mucosa
8. Development of malignancy *(endometrioid and clear cell carcinoma)* - uncommon.

(Ref: Robbins/10th/1004; Harsh Mohan/7th/722; Pathoma Lecture Notes)

Q. What is pseudosyesis? (RMU-22M)

Ans.

Pseudosyesis: Pseudocyesis (false pregnancy) is the appearance of clinical or subclinical signs and symptoms associated with pregnancy although the individual is not physically carrying a baby.

Q. What is chocolate cyst? (CU-12Ja, RU-10Ju) ***(Important for VIVA)***
Q. Explain chocolate cyst. (CU-18Nv)
Q. Short note: Chocolate cyst of ovary. (RU-17Nv,13Ju,07Ja, SU-13Ju)

Ans.

Chocolate cyst: Endometriotic lesions bleed periodically in response to both extrinsic cyclic (ovarian) and intrinsic hormonal stimulation. This bleeding produces nodules with a red-blue to yellow brown appearance on or just beneath the serosal surfaces and organizing hemorrhage causes extensive fibrous adhesions between tubes, ovaries, and other structures and obliterates the pouch of Douglas.

The ovaries may become markedly distorted by large cystic masses (3 to 5 cm in diameter) filled with **brown fluid** resulting from previous ***hemorrhage***; these are often referred to clinically as **chocolate cysts** or **endometriomas.**

(Ref: Robbins/10th/1006)

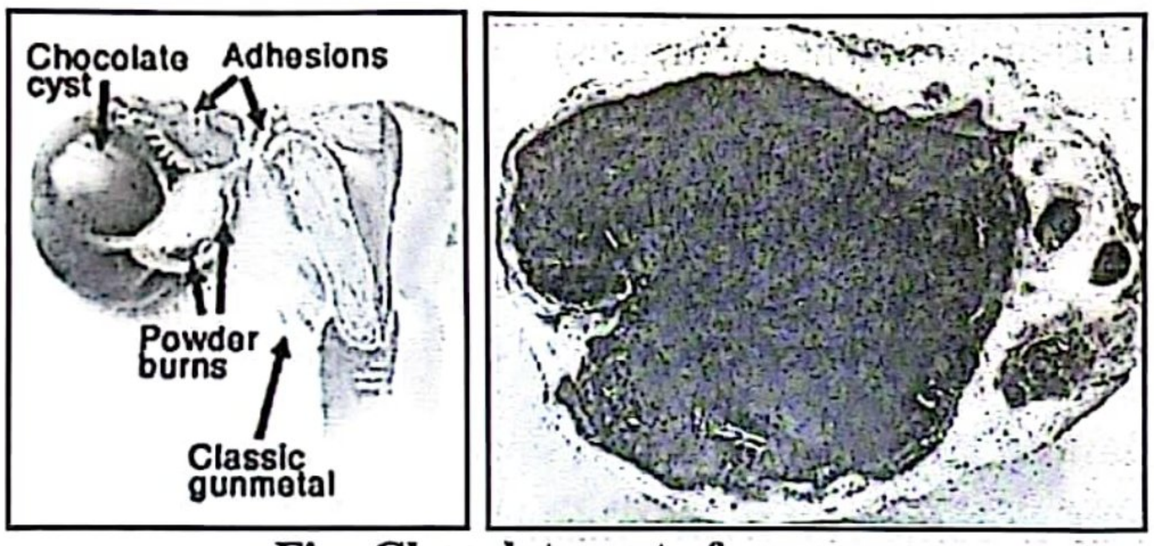


Fig: Chocolate cyst of ovary.

Q. A 25 year old woman present to your office for work up of infertility. In giving a history she describes a severe pain during mense, and she also tell you that in the past another doctor told her that she had "chocolate in her cysts". What abnormalities most likely to be present in this patient? Name the organ where chocolate cyst occurs. (DU-08Ja)

Ans.

Provisional diagnosis: Chocolate cyst of ovary.

Possible abnormalities:

- Severe dysmenorrhoea
- Dyspareunia
- Pelvic pain
- Menstrual irregularities
- Infertility.

Organ where chocolate cyst occurs: Ovary.

(Ref: Robbins/10th/1006)

Q. What do you mean by adenomyosis? (CMU-22Nv,19M, RMU-22Nv,20M,18Ja,09Ju)
Q. Mention complications of adenomyosis. (RU-19Nv)
Q. Write in brief about adenomyosis. (RMU-21Nv,17M,10Ju)
Q. Short note: Adenomyosis. (RU-19M,15Ju,07Ja)
Ans.
Adenomyosis: Adenomyosis is defined as the **presence of endometrial tissue within the uterine wall (myometrium)**. It occurs in up to 20% of uteri.

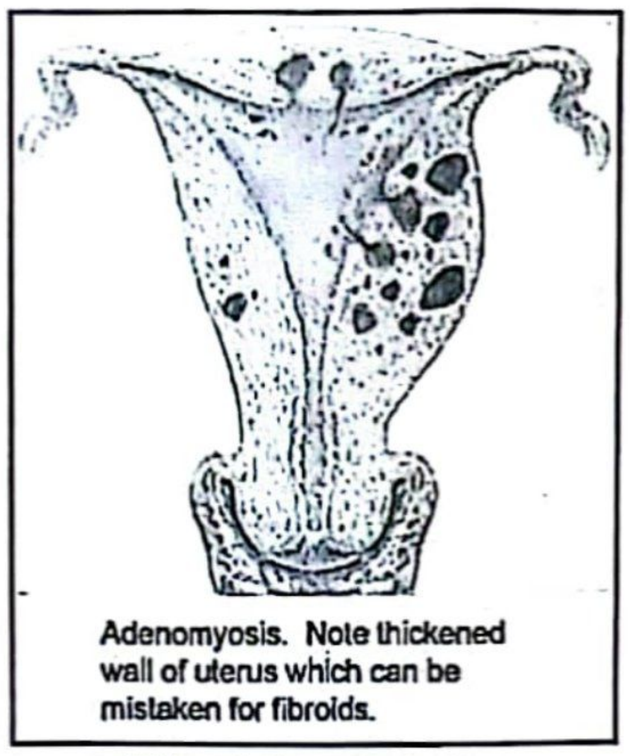


Fig: Adenomyosis.

Diagnosis: On microscopic examination, irregular nests of endometrial stroma, with or without glands, are arranged within the myometrium, separated from the basalis by at least 2 to 3 mm.

Clinical features / complications:

- Menometrorrhagia (irregular and heavy menses)
- Colicky dysmenorrhea
- Dyspareunia
- Pelvic pain (particularly during the menstrual period).

(Ref: Robbins/10th/1006)

(N.B: Adenomyosis can coexist with endometriosis).

(Ref: Robbins/10th/1006)

Q. Write the pathology of endometrial hyperplasia.
Q. Short note: Endometrial hyperplasia.
Ans.
Endometrial hyperplasia: It is defined as an **abnormal proliferation of the endometrial glands relative to the stroma**, resulting in an **increased gland-to-stroma ratio** when compared with normal proliferative endometrium.

Cause: Endometrial hyperplasia is associated with ***prolonged estrogenic stimulation of the endometrium***, which in turn may be caused by-

- Anovulatory cycles
- Obesity (peripheral conversion of androgens to estrogens)
- Menopause
- Polycystic ovarian syndrome
- Functioning granulosa cell tumors of the ovary
- Excessive ovarian cortical function (cortical stromal hyperplasia)
- Prolonged administration of estrogenic substances (estrogen replacement therapy)

Presentation: Classic presentation is ***postmenopausal uterine bleeding***.

Types: The most current WHO classification divides endometrial hyperplasia into two major categories (based on presence or absence or cellular atypia):

1. **Non-atypical (typical) hyperplasia:**
   - There is no cellular atypia
   - Cardinal feature is an increase in the gland-to-stroma ratio
   - Glands show variation in size and shape and may be dilated
   - Rarely progress to carcinoma i.e. low malignant potential (approximately 1% to 3%)

2. **Atypical hyperplasia (endometrial intraepithelial neoplasia** or **carcinoma *in situ*):**
   - Presence of 'atypical cells' in the hyperplastic epithelium
   - The extent of cellular atypia may be mild, moderate or severe
   - The cytologic features present in these cells include loss of polarity, large size, irregular and hyperchromatic nuclei, prominent nucleoli, and altered nucleo-cytoplasmic ratio
   - The glands are commonly back-to-back and often have complex outlines due to branching structures.
   - It is a precancerous condition and is associated with an increased risk of endometrial adenocarcinoma (23% to 48%).

Major complication: It is a frequent ***precursor to the most common type of endometrial carcinoma*** (the risk of carcinoma varies with the degree of cellular atypia).

(Ref: Robbins/10th/1006; Harsh Mohan/7th/723; BRS Pathology/5th/302; Pathoma Lecture Notes)

Q. What are the risk factors for endometrial carcinoma?

Ans.

Risk factors for endometrial carcinoma:

- Age – more than 40 years. Peak incidence in 55-65 years.
- Obesity
- Diabetes
- Hypertension
- Infertility
- Unopposed estrogen stimulation
- Endometrial hyperplasia.

(Ref: Robbins/9th/1020)

Nice to Know:

Endometrial carcinoma** is the **most common invasive cancer of the female genital tract.** Although it may be asymptomatic for a period of time, it usually produces **irregular or postmenopausal vaginal bleeding** with **excessive leukorrhea.

(Ref: Robbins/9th/1014,1018)

Q. A 60 years old female presented with irregular pervaginal bleeding for one month after menopause. Her P/V examination reveal apparently healthy cervix but with bloody discharge. What is your provisional diagnosis? How can you confirm it? (DU-17M)

Ans.

Clinical diagnosis: Endometrial carcinoma. *(It is the most common cause of irregular per-vaginal bleeding after menopause – the peak incidence is in 55-65 years)*

Investigations for confirmation of diagnosis:

- Trans-vaginal ultrasound
- Endometrial biopsy followed by histopathology
- Dilatation & curettage (if endometrial biopsy is non-diagnostic)
- Cytodiagnosis - Pap test (limited sensitivity – as low as 40%)
- Chest x-ray, CT scan / MRI of abdomen & pelvis - for staging
- Tumour marker: Serum CA-125 (elevated in 60% cases).

Q. A female of 60 complains of post-menopausal bleeding. USG examination of uterine cavity reveal marked thickening of endometrium. What is the clinical diagnosis? How will you confirm it? (DU-16Ju)

Ans.

Clinical diagnosis: Endometrial carcinoma.

Investigations for confirmation of diagnosis:

- Trans-vaginal ultrasound
- Endometrial biopsy followed by histopathology
- Dilatation & curettage (if endometrial biopsy is non-diagnostic)
- Cytodiagnosis - Pap test (limited sensitivity – as low as 40%)
- Chest x-ray, CT scan / MRI of abdomen & pelvis - for staging
- Tumour marker: Serum CA-125 (elevated in 60% cases).

Q. A 60 years old female presented with irregular per-vaginal bleeding for one month after menopause. She has been suffering from Diabetes Mellitus for last 10 year and her blood pressure is 140/90 mm of Hg. How will you precede to diagnosis such a patient? (DU-09Ja)

Ans.

Provisional diagnosis: Endometrial carcinoma.

Laboratory diagnosis:

- Trans-vaginal ultrasound
- Endometrial biopsy followed by histopathology
- Dilatation & curettage (if endometrial biopsy is non-diagnostic)
- Cytodiagnosis - Pap test (limited sensitivity – as low as 40%)
- Chest x-ray, CT scan / MRI of abdomen & pelvis - for staging
- Tumour marker: Serum CA-125 (elevated in 60% cases).

Q. Describe the pathology/ morphology of leiomyoma of uterus. (CMU-22M,21/19/18Nv, RU-17M, SU-10Ja)

Q. Describe the morphology of fibroid uterus. (SU-10Ja)

Q. Write about leiomyoma. (RU-19M)

Q. Short note: Leiomyoma. (RU-14Ja)

Ans.

Leiomyoma (fibroid) of uterus: Uterine leiomyomas (commonly called ***fibroid***) are the ***benign smooth muscle neoplasms of the uterus*** and perhaps the ***most common tumours in women***. These benign tumours may be present in about 75% of females of reproductive age. It may occur singly, but more often are multiple.

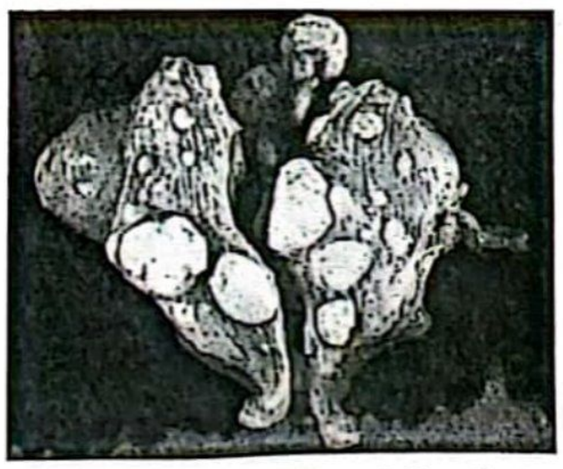
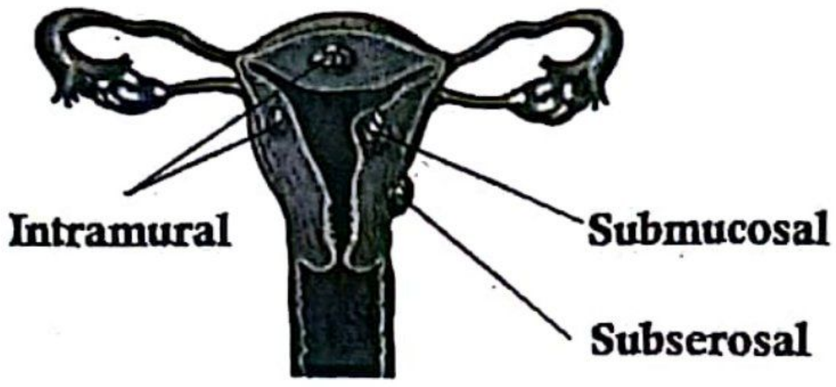


Fig: Leiomyoma (fibroid) of uterus.

Pathology / morphology:

Grossly:

- Sharply circumscribed, discrete, round, firm, gray-white tumor of varying sizes from small, barely visible nodules to massive tumors that fill the pelvis.
- Except in rare instances, they are found within the myometrium of the corpus.
- They can occur within the myometrium (**intramural**), just beneath the endometrium (**submucosal**), or beneath the serosa (**subserosal**).
- On cut section, they exhibit characteristic ***whorled pattern***
- Large tumors may develop areas of yellow-brown to red softening (red degeneration).



Uterine fibroid

Fig: Different varieties of fibroid uterus.

Histologically:

- They are essentially composed of 2 tissue elements—whorled bundles of smooth muscle cells admixed with variable amount of connective tissue.
- Individual smooth muscle cells are uniform in size and shape with abundant cytoplasm and central oval nuclei
- Mitotic figures are scarce.

(Ref: Robbins/10th/1014)

*{**N.B: Leiomyomas are also found** in arrector pili (pilar leiomyoma – very painful), nipples, scrotum, labia & less frequently deep soft tissue and gut wall}.*

(Ref: Lecture SSMC)

Q. Mention the complications of leiomyoma (fibroid uterus). (RMU-23/21M,20/19Nv,17Ju/M,16Ju, 12Ja,10/09Ju,05Ja)

Ans.

Complication of leiomyoma:

1. Abnormal uterine bleeding
2. Urinary frequency due to compression of the bladder
3. Sudden pain (from infarction of a large or pedunculated tumor)
4. Impaired fertility
5. In pregnant women-
   - Increase the frequency of spontaneous abortion
   - Fetal malpresentation
   - Uterine inertia (failure to contract with sufficient force)
   - Postpartum hemorrhage
6. Malignant transformation to leiomyosarcoma - extremely rare.

(Ref: Robbins/10th/1014)

Q. A lady of 35 years gave the H/O increased menstrual bleeding for last 3 months. USG finding is a sub-mucosal mass in uterine cavity. Give your diagnosis & how will you confirm it? (RMU-23M)

Q. A female of 40 years gives the history of lower abdominal pain, excessive per-vaginal bleeding for 06 months. USG shows a mass in the uterus. (BUP-18M)

a) **What is your probable diagnosis?**
b) **Give the features of identification of the lesion.**

Q. A lady of 36 years gives H/O of increased menstrual blood loss for the last 3 months. USG of lower abdomen shows a sub-mucosal mass in her uterine cavity. The mass was removed. Cut section of mass revealed whorled appearance. (BUP-17M)

a) **What is your probable diagnosis?**
b) **How can you confirm it?**

Ans.

Probable diagnosis: Fibroid uterus (leiomyoma of uterus).

Identifying features of the lesion: *Please write from above* (morphology).

Confirmation: Histopathological study of the surgically resected mass.

Ovaries

Q. Classify ovarian tumors. (DU-18/14/06Ja, BUP-22Nv, CMU-22Nv,12Ja, RU-08Ja, SU-16Ja,06S)

Q. Mention the WHO classification of ovarian neoplasms. (SU-20M)

Q. Classify surface epithelial tumors of ovary. (RU-20M)

Q. Classify surface epithelial-stromal tumors of ovary. (DU-16Ja, RU-16Ju,10Ja)

Q. Classify ovarian surface epithelial neoplasm. (RMU-22/19M)

Q. Classify sex-cord stromal tumors of ovary. (CU-19M)

Q. Classify / enumerate the germ cell tumors of ovary. (RMU-23M,21/20/19/18Nv,17Nv/Ja,15/14/12/11Ja, SU-22Nv,14Ja,09Ju, BUP-21Nv/M, CU-19Nv,15Ju,05Ja)

Q. Name five benign surface tumors of ovary. (SU-09Ja)

Ans.

WHO classification of ovarian tumors: ***(Important for VIVA)***

(A simplified classification proposed by the WHO with widely adopted minor modifications)

A. **Surface epithelial tumors:** (3/4th of ovarian tumors)

   a. **Serous tumors:**
      - Benign (serous cystaden*oma*)
      - Borderline (serous borderline tumor)
      - Malignant (serous cystadeno*carcinoma*) - 50% of ovarian carcinomas

   b. **Mucinous tumors (endocervical-like & intestinal type):**
      - Benign (mucinous cystaden*oma*)
      - Borderline (mucinous borderline tumor)
      - Malignant (mucinous cystadeno*carcinoma*)

   c. **Endometrioid tumors:**
      - Benign (endometroid cystaden*oma*)
      - Borderline (endometroid borderline tumor)
      - Malignant (endometroid adeno*carcinoma*)

   d. **Clear cell tumors:**

- Benign
- Borderline
- Malignant (clear cell adenocarcinoma)

e. Brenner tumors (transitional cell tumors):

- Benign Brenner tumor
- Brenner tumor of borderline malignancy
- Malignant Brenner tumor

B. <u>Germ cell tumors</u>: Nearly 95% are benign and occur chiefly in females younger than 20 years of age.

a. Dysgerminoma
b. Teratoma:
   - Benign (mature / adult) teratoma: Solid, cystic (dermoid cyst)
   - Malignant (immature) teratoma
   - Monodermal or specialized teratoma (e.g. struma ovarii, carcinoid tumour)
c. Endodermal sinus (yolk sac) tumor
d. Choriocarcinoma
e. Others (embryonal carcinoma, polyembryoma, mixed germ cell tumors)

C. <u>Sex-cord stromal tumors</u>:

a. Granulosa-theca cell tumours
   - Granulosa cell tumors
   - Fibromas
   - Thecomas
   - Fibrothecomas

b. Sertoli-Leydig cell tumors (Androblastoma, Arrhenoblastoma)

c. Steroid (lipid) cell tumors

D. Malignant, not otherwise specified

E. Metastatic cancer from non-ovarian primary (Krukenberg tumour & others)

- Colonic, appendiceal
- Gastric
- Pancreaticobiliary
- Breast.

(Ref: Robbins/10th/1017; BRS Pathology/5th/304-307; Harsh Mohan/7th/731)

<u>Nice to Know</u>:

- **Benign tumors** are composed of well-differentiated epithelial cells with minimal proliferation.
- **Borderline tumors** show increased cell proliferation, but lack stromal invasion.
- **Malignant tumors** show increased epithelial atypia and are defined by the presence of stromal invasion.

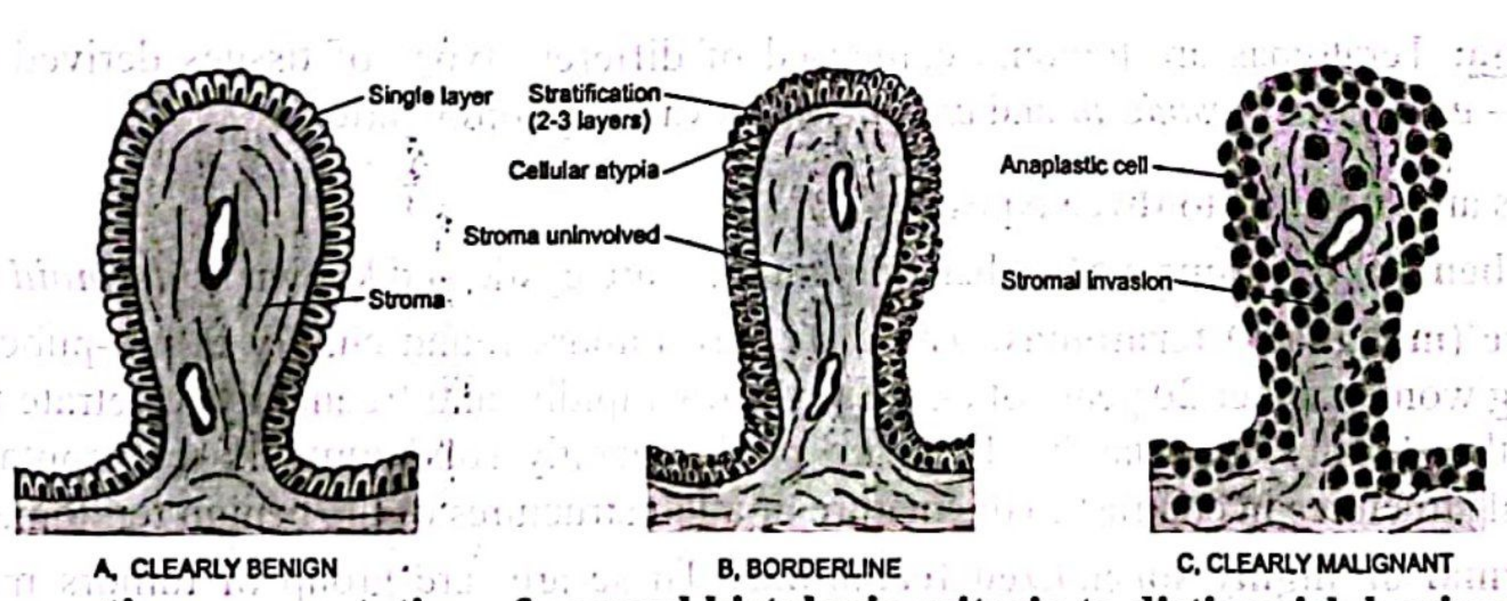


Fig: Diagrammatic representation of general histologic criteria to distinguish benign, borderline (atypical proliferating) and malignant surface epithelial tumours of the ovary.

(Ref: Robbins/10th/1017; Harsh Mohan/7th/732)

Q. Classify ovarian cysts. (SU-22Nv/M,19M,12/11Ja)
Q. Enumerate the causes of cystic mass in the ovary. (SU-05Ja)
Q. Name the non-neoplastic cysts of ovary. (RU-17Nv,14Ja, SU-13Ju/Ja)
Ans.

Classification of ovarian cysts: ***(Important for VIVA)***

1. **Non-neoplastic and functional cysts:**
   - Follicular cysts
   - Leuteal cysts
   - Chocolate cyst (ovarian endometrioma)
   - Polycystic ovarian disease / Polycystic ovarian syndrome (PCOS)
2. **Neoplastic cysts:**
   - ***Surface epithelial tumors*:**
     - Serous or mucinous cystaden*oma*
     - Serous or mucinous cystaden*ocarcinoma*
   - ***Germ cell tumors*:** Mature cystic teratoma (dermoid cyst).

(Ref: Robbins/10th/1016; Harsh Mohan/7th/731)

Nice to Know:

Polycystic ovarian syndrome (PCOS) (formerly called ***Stein Leventhal syndrome***): It is a complex endocrine disorder characterized by hyperandrogenism, menstrual abnormalities, polycystic ovaries, chronic anovulation, and decreased fertility.

(Ref: Robbins/10th/1016)

Or,

Polycystic ovary syndrome (PCOS) is a syndrome characterized by oligomenorrhoea, anovulation, infertility, hirsutism and obesity in young women having bilaterally enlarged and cystic ovaries.

(Ref: Harsh Mohan/7th/730)

It is also associated with obesity, type 2 diabetes, and premature atherosclerosis.

Pathophysiology: The principal biochemical abnormalities in most patients are excessive production of androgens, and low levels of pituitary follicle stimulating hormone (FSH). FSH is inhibited to low levels by testosterone but the level of LH is sufficient to cause luteinisation of ovarian theca and granulosa cells which then secrete androgen inappropriately and produce an abnormal state of anovulation. A hereditary basis for the syndrome has been suggested in some cases.

(Ref: Robbins/10th/1016; Harsh Mohan/7th/730)

Q. Give an account of ovarian teratoma. (CMU-22M,05Ja, SU-14Ja,09Ju, RU-08Ja)
Q. Classify ovarian teratoma. (SU-15Ju)
Ans.

Ovarian teratoma: Teratomas are tumours composed of different types of tissues derived from the **three germ cell layers**—***ectoderm***, ***mesoderm*** and ***endoderm***, in varying combinations.

Types: Teratomas are divided into **three** types-

1. **Mature (benign) teratomas:** Most benign teratomas are cystic and known as ***dermoid cysts***.
2. **Immature (malignant) teratomas:** These are rare tumors found chiefly in pre-pubertal adolescents and young women under 20 years of age. They grow rapidly, and frequently penetrate the capsule, and spread either locally or distantly. They are predominantly solid tumours that contain immature or embryonal structures in contrast to the mature or adult structures of the benign teratomas.
3. **Monodermal or highly specialized teratomas:** These are rare group of tumors most common of which are **struma ovarii** and **carcinoid**.

(Ref: Robbins/10th/1023)

Q. What is struma ovarii? (RU-18M)

Ans.

Struma ovarii: A struma ovarii (literally: **goitre of the ovary**) is a rare form of specialized or monodermal teratoma that contains mostly **thyroid tissue,** which may cause **hyperthyroidism.**

Thyroid tissue must comprise more than 50 percent of the overall tissue to be classified as a struma ovarii.

Struma ovarii accounts for approximately 5 percent of all ovarian teratomas. The vast majority of struma ovarii are benign tumors; however, malignant tumors of this type is found in a small percentage of cases.

(Ref: BRS Pathology/5th/306; Robbins/10th/1024; Harsh Mohan/7th/737)

Q. Give the brief description of dermoid cyst of ovary. (SU-13/12/11Ja)
Q. Describe the morphology of dermoid cyst of ovary. (DU-06Ja, BUP-21Nv/M, SU-22/21/19M,16/07Ja, CU-17M,12Ja, RU-12Ju)
Q. Write down the microscopic features of dermoid ovary. (RU-20M)
Q. Short note: Benign cystic teratoma of ovary.
Q. Short note: Dermoid cyst of ovary. (DU-22Nv,11Ju,10Ja, SMU-23M,19Nv,05Ja, RU-09/07Ja)
Q. Short note: Dermoid cyst. (DU-22M, RMU-23M)

Ans. ***(Important for VIVA)***

Benign cystic teratoma (dermoid cyst): Benign cystic teratomas are often referred to as ***dermoid cysts,*** because they are almost always **lined by *skin-like structures*.**

They account for approximately 20% of ovarian tumours and 90% of germ cell tumours. They are the most frequent benign ovarian tumours, and are usually found in young women during their active reproductive life.

Morphology:

***Macroscopic*:**

- They are bilateral in 10% to 15% of cases.
- They are **unilocular cysts** containing **hair & cheesy sebaceous material.**
- The cyst wall is thin and opaque grey-white, wrinkled, **apparent epidermis.**
- From this epidermis, **hair shafts** frequently protrude.
- Within the wall, **tooth structures & areas of calcification** are present.

***Microscopic*:**

- The cyst wall is lined by **skin,** including **hair follicles** & other **skin appendages.**
- Structures from other germ layers can be identified, such as **cartilage, bone, gastrointestinal, neural, respiratory** and **thyroid gland** tissues.

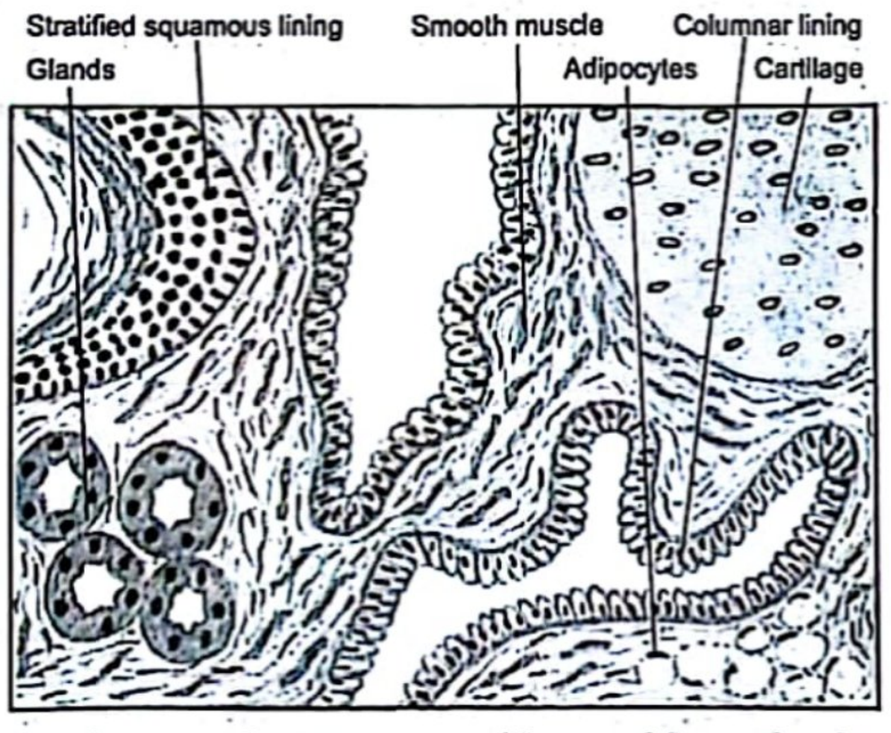


Fig: Benign cystic teratoma (dermoid cyst) of ovary.

Chance of malignancy: About 1 % may give rise to-

- Squamous cell carcinoma (*most common*)

- Thyroid carcinoma
- Melanoma.

(Ref: Robbins/10th/1023; BRS Pathology/5th/306; Harsh Mohan/7th/736)

Q. Give the components of a dermoid cyst. (DU-18Ja)

Ans.

Components of a dermoid cyst (benign cystic teratoma):

- The cyst is lined by skin, including hair follicles & other skin appendages like sebaceous gland, sweat glands etc.
- Various other tissue components frequently found in teratomas are bone, tooth, cartilage, smooth muscle, gastrointestinal, pancreatic, neural, retinal, respiratory, salivary gland and thyroid gland tissues.

(Ref: Robbins/10th/1023; BRS Pathology/5th/306; Harsh Mohan/7th/737)

Q. Give the morphology of dysgerminoma. (RMU-23/21M,14Ja,12Ju, CU-18Nv,05Ja)
Q. Write about dysgerminoma. (RU-19Nv)
Q. Short note: Dysgerminoma of ovary. (RU-18Ja,17Nv,08Ju)

Ans.

Dysgerminoma: Dysgerminoma is a germ cell tumour of ovary, and is best considered as the ***ovarian counterpart of the seminoma of the testis***. It comprises about 2% of all ovarian cancers and about half of malignant germ cell tumors.

About 10% of patients with dysgerminoma have elevated **β-hCG** level in the plasma. All dysgerminomas are malignant and are extremely radiosensitive.

Age of incidence: They may occur in childhood, but 75% occur in the 2nd & 3rd decades.

Morphology:

***Grossly*:**

- Usually unilateral (80 - 90%).
- They are solid tumors.
- They vary in size from barely visible nodules to masses that virtually fill the entire abdomen.
- On cut surface, they have a yellow-white to gray-pink appearance and are often soft & fleshy with foci of haemorrhage and necrosis.

***Histologically*:**

- The tumour cells are arranged in diffuse sheets, islands and cords separated by scanty fibrous stroma.
- Fibrous stroma is infiltrated with mature lymphocytes & occasional granulomas.
- On occasion, small nodules of dysgerminoma are encountered in the wall of an otherwise benign cystic teratoma; conversely, a predominantly dysgerminomatous tumor may contain a small cystic teratoma.

(Ref: Robbins/10th/1024; Harsh Mohan/7th/737)

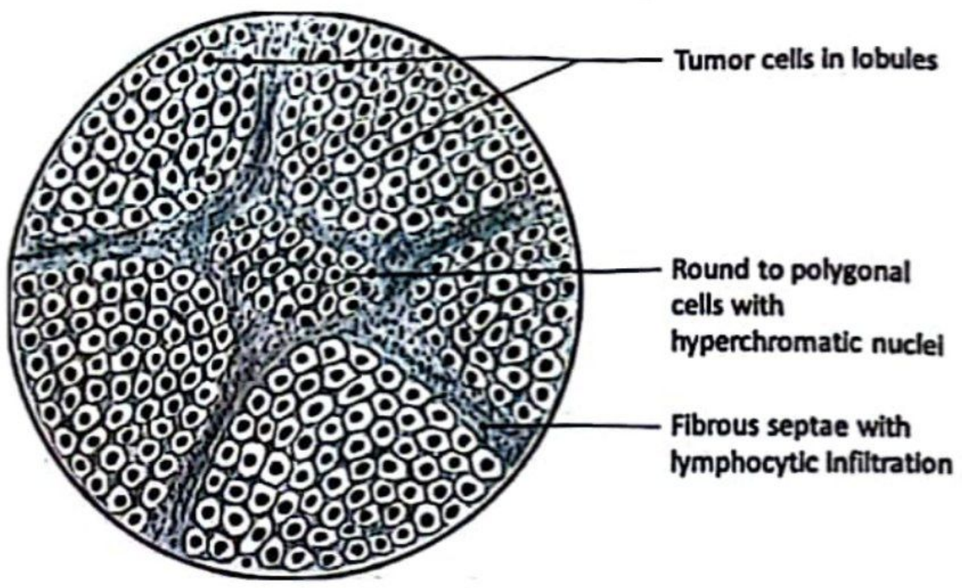

Tumor cells in lobules
Round to polygonal cells with hyperchromatic nuclei
Fibrous septae with lymphocytic infiltration

Fig: Dysgerminoma of ovary.

Nice to Know:

Choriocarcinoma: Choriocarcinoma in females is of 2 types—***gestational*** (placental origin) and ***non-gestational.***

Ovarian (*non-gestational*) choriocarcinoma is more malignant than that of placental origin and disseminates widely via bloodstream to the lungs, liver, bone, brain and kidneys. The marker for both types of choriocarcinoma is hCG.

In contrast to choriocarcinomas arising in placental tissue, those arising in the ovary are generally unresponsive to chemotherapy and are often fatal.

(Ref: Robbins/10th/1025; Harsh Mohan/7th/737)

Q. What are the hormone producing tumors of ovary? (RMU-22Nv, SU-22/21M)

Ans.

Hormone producing tumors of ovary:

1. **Granulosa-theca cell tumors:** Secrete estrogen.
2. **Sertoli-Leydig cell tumors** (Androblastomas, Arrhenoblastoma)**:** Secretes androgen.
3. **Choriocarcinoma:** Secretes human chorionic gonadotropin (HCG)
4. **Others:** Struma ovarii, carcinoid, hilar cell tumour.

(Ref: Robbins/10th/1016-1028; BRS Pathology/5th/307; D.C. Dutta Gynaecology)

Q. What are the origins of metastatic tumors of ovary?

Ans.

Origin of metastatic tumors of ovary:

- **Mullerian origin:** Uterus, fallopian tube, contralateral ovary, or pelvic peritoneum.
- **Extra-mullerian origin:** Breast, GI tract (including colon, stomach, biliary tract, pancreas), and pseudomyxoma peritonei derived from appendiceal tumors.

(Ref: Robbins/10th/1028; Harsh Mohan/7th/1034)

Q. What do you mean by Krukenberg tumor? (RMU-21M) ***(Very Important for VIVA)***

Q. Short note: Krukenberg tumor. (RU-19M,15Ja,12Ju,10Ja)

Ans.

Krukenberg tumor: A classic **metastatic gastrointestinal carcinoma involving the ovaries** is termed as *Krukenberg tumor*.

Characteristics: Krukenberg tumor is characterized by **bilateral metastases** composed of **mucin-producing cancer cells** with a **"signet-ring"** appearance, most often of **gastric origin**. It may also arise from **breast**, **lung** etc.

(Ref: Robbins/10th/1028; BRS Pathology/5th/307; Harsh Mohan/7th/1034)

Q. What is Meigs syndrome? (RU-18Nv) ***(Important for VIVA)***

Q. Short note: Meigs syndrome. (RU-18Ja,17Nv,16Ja,14/12/11Ju,10Ja)

Ans.

Meigs syndrome: The triad of ***ovarian fibroma***, ***ascites*** and ***hydrothorax*** (usually only of right side) is designated as ***Meigs syndrome***. Its genesis is unknown.

The ascites and pleural effusion resolve spontaneously when the ovarian tumour is removed.

(Ref: Robbins/10th/1027; BRS Pathology/5th/306; D.C. Datta/5th/616)

Q. List the tumour markers associated with ovarian tumour. (DU-16/14Ja)

Ans.

Tumour markers associated with ovarian tumour: ***(Very Important for VIVA)***

1. **Epithelial ovarian cancer:**
   - CA-125 (most common)
   - CA-72-4
   - CA-19-9
   - CEA (carcinoembryonic antigen)

2. **Germ-cell tumours:**
   - Serum α-fetoprotein (AFP)
   - Serum β-hCG

3. **Sex-cord stromal tumours:**
   - Estradiol (a type of estrogen) and inhibin.

Q. Write down the laboratory diagnosis of ovarian tumour. (CU-20M)

Ans.

Laboratory diagnosis of ovarian tumour:

1. CBC, liver function tests, renal function tests
2. Serum tumour markers
   - CA-125 (for epithelial carcinoma)
   - α-fetoprotein (AFP) & β-hCG (for germ cell tumour)
   - CEA & CA-19-9 (to rule out the secondaries / metastatic ovarian tumour).

Q. A female of 22 years presented with a intra-abdominal swelling having USG evaluation of unilateral ovarian tumour. Write your differential diagnosis. What are the laboratory tests you can suggest to evaluate it. (CU-20M)

Ans.

Differential diagnosis:

1. **Benign**
   - **Non-neoplastic:** Functional ovarian cysts e.g. follicular &corpus luteal cysts, PCOS etc.
   - **Neoplastic:** Benign ovarian tumour e.g. benign surface epithelial, germ cell and sex-cord stromal tumours.

2. **Malignant**
   a. **Primary**
      - Surface epithelial tumours
        - Serous cystadeno*carcinoma*
        - Mucinous cystadeno*carcinoma*
        - Endometroid *carcinoma*
        - Clear cell carcinoma
        - Malignant Brenner tumor
        - Mixed epithelial tumour
      - Germ cell tumours
        - Dysgerminoma
        - Endodermal sinus (yolk sac) tumor
        - Embryonal carcinoma
        - Polyembryoma
        - Choriocarcinoma
        - Teratoma
        - Mixed germ cell tumors

- Sex cord stromal tumours
  - Granulosa-theca cell tumours
  - Sertoli-Leydig cell tumors
  - Steroid (lipid) cell tumors
- Other non-specific soft tissue tumours

b. Secondary (Krukenberg tumour & others).

Laboratory tests: *Please write from above.*

CHAPTER 11

GESTATIONAL TROPHOBLASTIC DISEASE

Q. Enumerate the gestational trophoblastic diseases. (RU-12Ju)
Q. What are the gestational trophoblastic tumors?
Q. Short note: Gestational trophoblastic disease. (RU-10Ja)
Ans.
Gestational trophoblastic tumors: Gestational trophoblastic disease encompasses a spectrum of tumors and tumorlike conditions characterized by proliferation of placental tissue, either villous or trophoblastic.

The major disorders of this type are:

1. Hydatidiform mole (complete and partial)
2. Invasive mole
3. Placental-site trophoblastic tumor (PSTT)
4. Choriocarcinoma (frankly malignant).

(Ref: Robbins/10th/1033)

Q. Mention morphology of hydatidiform mole. (CU-12Ju)
Q. Short note: Hydatidiform mole. (SU-20Nv) ***(Very Important for VIVA)***
Ans.
Hydatidiform mole: Hydatidiform mole is characterized by **cystic swelling of the chorionic villi,** accompanied by variable trophoblastic proliferation. They are associated with an increased risk of persistent trophoblastic disease (**invasive mole**) or **choriocarcinoma**.

They are usually diagnosed during early pregnancy (average 9 weeks) by pelvic sonography.

Age of incidence: Molar pregnancy can develop at any age, but the risk is higher at the two ends of reproductive life, in teenagers and between 40 and 50 years of age.

Clinical characteristics:

- Vaginal bleeding
- Spontaneous miscarriage
- Rapid increase in uterine size

A hydatidiform mole ***can be mistaken for a normal pregnancy***, but the uterus is often ***too large for the supposed state of gestation***. **Human chorionic gonadotropin (hCG)** levels also greatly ***exceed those of a normal pregnancy of similar gestational age***.

Clinical variants: It occurs in two variants:

(1) **Complete hydatidiform mole:** No embryo is present; **46,XX** karyotype, of exclusively **paternal derivation** (a phenomenon called **androgenesis**).

(2) **Partial hydatidiform mole:** Embryo is present; **triploidy** (e.g. 69,XXY) and **rarely tetraploidy** (92,XXXY) occur, thought to be due to fertilization of the ovum by two or more spermatozoa. The usual result is **69 chromosomes** derived from **two paternal** and **one maternal** haploid set.

Morphology:

***Macroscopic*:**

- Uterine cavity is filled with a delicate, friable mass of thin-walled, translucent, cystic, grape-like structures consisting of swollen edematous (hydropic) villi.
- Fetal parts are frequently seen in partial moles.

***Microscopic*:**

- **Complete moles** show abnormalities that involve ***all or most of the villous tissue***. The chorionic villi are enlarged, scalloped in shape with central cavitation (cisterns), and lack adequately developed vessels.
- **Partial moles** show ***only a fraction of the villi*** are enlarged and edematous, and the trophoblastic hyperplasia is focal and less marked than in complete moles.

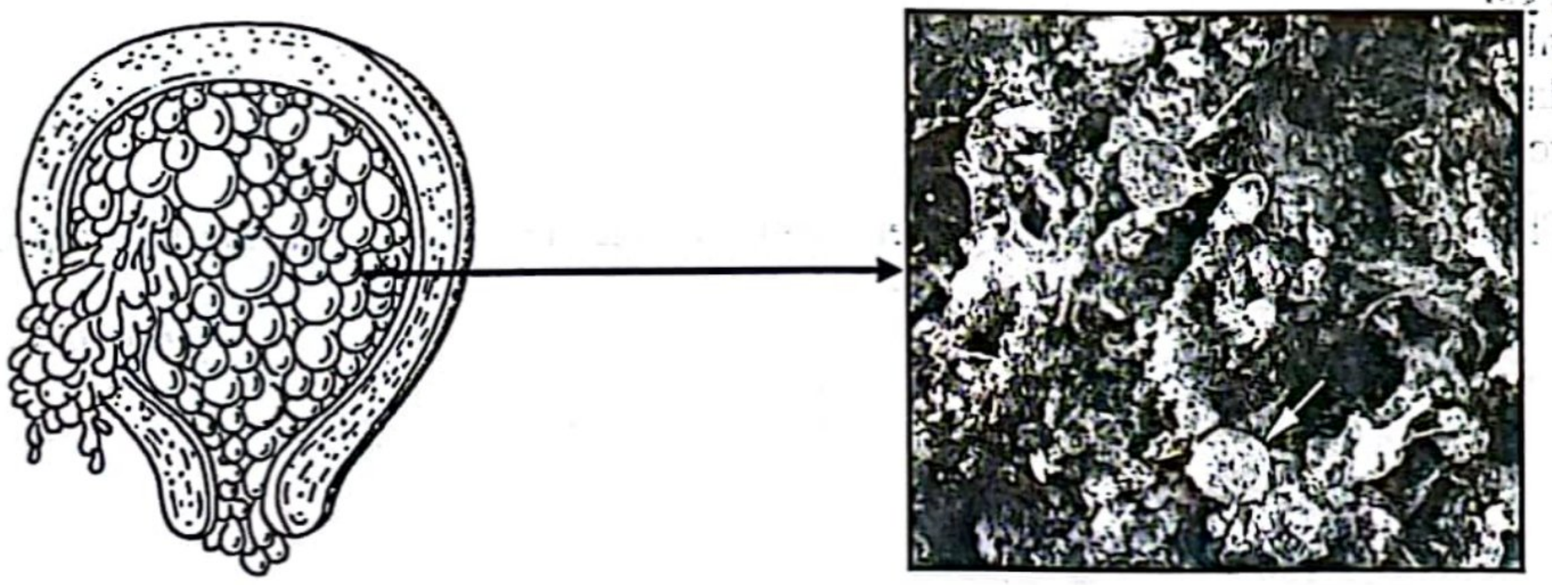


Fig: Complete hydatidiform mole.

(Ref: Robbins/10th/1033; BRS Pathology/5th/310)

Q. Mention the differences between complete mole and partial mole. *(Important for VIVA)*

Ans.

Differences between complete mole and partial mole:

Traits	Complete mole	Partial mole
1. Karyotype	Diploid (46 XX or 46 XY)	Triploid (69 XXY or 69 XXX)
2. Fertilization	2 sperm + empty egg	2 sperm + 1 egg
3. Fetal tissue	Absent	Present
4. Blood vessel	Absent	Present
5. Hydropic villi	More edematous hydropic villi	Few hydropic villi

(Ref: Lecture DMC)

Q. How hydatidiform mole can be diagnosed in the laboratory? (SU-06/05Ja)

Ans.

Laboratory diagnosis of hydatidiform mole:

1. **Ultrasonogram (USG)** reveals snowstorm appearance of the mole (diagnostic)

2. **Serum level of HCG** is markedly elevated
3. **X-ray chest:** to exclude metastatic choriocrcinoma
4. **Urine:**
   - HCG level- elevated
   - Pregnancy test- positive (+ve)
5. **Biopsy:**
   a. **Macroscopic feature:** A mass of grape like structures of varying sizes filling the uterus
   b. **Microscopic feature:**
      - Marked proliferation of syncytial or cytotrophoblastic epithelium
      - Marked thinning of the stromal tissue due to accumulation of fluid
      - Absence of blood vessel
      - The villus pattern is distinctly maintained.

Q. Mention morphology of invasive mole. (CU-12Ju)
Q. Short note: Invasive mole.
Ans.
Invasive mole: Invasive mole is an infiltrative lesion that penetrates or even perforates the uterine wall.

Morphology: There is invasion of the myometrium by hydropic chorionic villi, accompanied by proliferation of both cytotrophoblast and syncytiotrophoblast. The tumor is locally destructive and may invade parametrial tissue and blood vessels. Hydifopic villi may embolize to distant sites, such as lungs and brain, but do not grow in these organs as true metastases, and even without chemotherapy they eventually regress.

Clinical features:
- Vaginal bleeding
- Irregular uterine enlargement
- Persistently elevated serum hCG.

Treatment: The tumor responds well to chemotherapy but may result in uterine rupture, necessitate hysterectomy.

(Ref: Robbins/10th/1034)

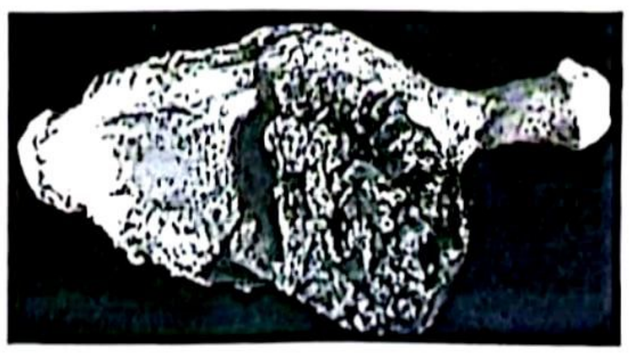


Fig: Invasive mole presenting as a hemorrhagic mass adherent to the uterine wall.

Q. Short note: Choriocarcinoma.
Ans.
Choriocarcinoma: Gestational choriocarcinoma is a **malignant neoplasm of trophoblastic cells** derived from a previously normal or abnormal pregnancy, such as an extrauterine ectopic pregnancy. It is rapidly invasive and metastasizs widely, but once identified responds well to chemotherapy.

It may be preceded by several conditions:
- 50% arise in complete hydatidiform moles
- 25% in previous abortions
- Approximately 22% follow normal pregnancies with the remainder occurring in ectopic pregnancies.

Fig: Choriocarcinoma presenting as a bulky hemorrhagic mass invading the uterine wall.

Morphology:

Macroscopic:

- It is a soft, fleshy, yellow-white tumour that usually has large pale areas of necrosis and extensive haemorrhage.

Microscopic:

- It consists entirely of proliferating syncytiotrophoblasts and cytotrophoblasts.
- Chorionic villi are absent.
- Mitoses are abundant and sometimes abnormal.
- The tumour invades the underlying myometrium, frequently penetrates blood vessels, and in some cases extends out onto the uterine serosa and into adjacent structures.

Clinical features: Irregular vaginal spotting of a bloody, brown fluid.

Metastases: Widespread metastases are characteristic; the most common sites are the lungs (50%) and vagina (30% to 40%), followed by, in descending order of frequency, the brain, liver, bone, and kidney.

(Ref: Robbins/10th/1034)

Q. A 3 month pregnant woman, 40 yrs age come with vaginal bleeding. Ultrasonogram of lower abdomen shows cystic changes in uterus and grape like clusters. What is your provisional diagnosis and most serious complication? (Important for VIVA)

Ans.

Provisional diagnosis: Hydatidiform mole.

Complication: Choriocarcinoma.

Q. What is psedocyesis? How can you differentiate urine of pregnant lady from urine of trophoblastic tumor by examining urine? (RU-07Ju)

Ans.

Psedocyesis: A condition in which a patient has nearly all of the usual signs and symptoms of pregnancy such as enlargement of the abdomen, weight gain, cessation of menses and morning sickness, but the patient is not pregnant. It is usually seen in women who either are very desirous of having children or wishes to avoid pregnancy. Treatment is usually done by psychiatric means.

Differentiation of urine of pregnant lady from urine of trophoblastic tumor by examining urine: The HCG level in pregnant women is below 1 lac unit but in trophoblastic tumor it is more than 1 lac and it may be up to 5 lacs.

CHAPTER 12

THE BREAST

The Female Breast

Q. Name the diseases of the breast. (CU-03Ja)
Q. What are the inflammatory conditions of breast?
Q. Classify tumors of the breast. (DU-23Nv, CMU-22Nv/M,19Nv,10Ju, SU-08/07Ju, RU-07Ju)
Q. Classify breast cancer / breast carcinoma. (DU-19Nv,14Ju, RMU-23/22/20/19M,16/11Ju, SU-20Nv, CU-18Nv,17M)
Q. Classify breast tumors including carcinoma breast. (RU-18M)
Q. Classify carcinoma of breast. (RMU-21/18M)
Q. Write down the histological classification of breast cancer. (CU-20/18M)
Q. Short note: Classification of carcinoma breast. (RU-17M)

Ans.

Diseases of breast:

1. **Congenital anomalies:**
   - Milk-line remnants (supernumerary nipples or breasts) – *most common congenital anomaly*
   - Accessory axillary breast tissue
   - Congenital nipple inversion
   - Amastia *(occurs in both sex & may be uni/bilateral)*
2. **Inflammatory disorders:**
   - Acute mastitis
   - Squamous metaplasia of lactiferous ducts / recurrent subareolar abscess / periductal mastitis / zuska disease
   - Duct ectasia
   - Fat necrosis
   - Lymphocytic mastopathy (sclerosing lymphocytic lobulitis)
   - Granulomatous mastitis (e.g. granulomatosis with polyangiitis, sarcoidosis, tuberculosis)
3. **Benign epithelial lesions:**
   - ***Non-proliferative breast changes (fibrocystic changes)***

- Cyst
- Fibrosis
- Adenosis

- ***Proliferative breast disease without atypia***
  - Epithelial hyperplasia
  - Sclerosing adenosis
  - Complex sclerosing lesion
  - Papillomas
  - Gynecomastia (enlargement of the male breast)
- ***Proliferative breast disease with atypia***
  - Atypical ductal hyperplasia
  - Atypical lobular hyperplasia

4. Tumors of breast: *(Important for VIVA)*

A. Benign tumours:

a. Stromal tumors:
- Fibroadenoma (most common)
- Phyllodes tumor (cystosarcoma phyllodes)
- Myofibroblastoma
- Lipomas

b. Epithelial tumors: Intraductal papilloma.

B. Malignant tumours:

i) Primary: Adenocarcinoma in >95% of cases.

a. Non-invasive (in situ carcinoma) (15-30%):
- Ductul carcinoma in situ (80%)
- Lobular carcinoma in situ (20%)

} ***Prognosis good as it is in situ / non-invasive***

b. Invasive (infiltrating) carcinoma (70-85%): WHO classification-
- Invasive ductul carcinoma (80%)
- Invasive lobular carcinoma (10%)
- Tubular (cribriform) carcinoma (6%)
- Medullary carcinoma (2%)
- Mucinous (colloid) carcinoma (2%)
- Papillary carcinoma
- Metaplastic carcinoma
- Inflammatory carcinoma

c. Paget disease of nipple

d. Angiosarcoma

e. Others:
- Malignancies arising from lymphocytes or skin of the breast, sweat glands, sebaceous glands, and hair shafts.
- Primary breast lymphoma (*Non-Hodgkin lymphoma).*

ii) Secondary (rare)**:** Metastases from a contralateral breast carcinoma, melanoma, lymphoma, lung and ovarian cancers.

(Ref: Robbins/10th/1037-1063; Harsh Mohan/7th/751; BRS Pathology/5th/311; Lecture SSMC)

Nice to Know:

Inflammatory disorders of breast:

- **Acute mastitis:** Acute bacterial mastitis typically occurs during the first month of breastfeeding and is caused by a local infection by *Staphylococcus aureus* or, less commonly, streptococci. The breast is erythematous and painful, and fever is often present.
- **Squamous metaplasia of lactiferous ducts:** It is known by a variety of names, including recurrent subareolar abscess, periductal mastitis, and Zuska disease. Women, and sometimes men, present with a painful erythematous subareolar mass that mimics a bacterial abscess. More than 90% of afflicted individuals are smokers.
- **Duct ectasia:** It presents as a palpable periareolar mass that is often associated with thick, white nipple secretions and occasionally with skin retraction. Pain and erythema are uncommon and not associated with cigarette smoking.
- **Fat necrosis:** The presentations of fat necrosis are protean and may closely mimic cancer. It may present as a painless palpable mass, skin thickening or retraction, or mammographic densities or calcifications. About half of affected women have a history of breast trauma or surgery.
- Lymphocytic Mastopathy (Sclerosing Lymphocytic Lobulitis): This condition presents with single or multiple hard palpable masses or mammographic densities. The masses are associated with areas of densely collagenized stroma, a feature that may make it difficult to obtain lesional tissue by needle biopsy. Within the stroma are atrophic ducts and lobules with thickened basement membranes that are surrounded by a prominent lymphocytic infiltrate.
- Granulomatous Mastitis: Granulomatous inflammation of the breast may be a manifestation of systemic granulomatous diseases (e.g., granulomatosis with polyangiitis, sarcoidosis, tuberculosis) or of inflammatory or infectious disorders that are localized to the breast.

(Ref: Robbins/10th/1040; Lecture SSMC)

Q. Mention the morphology of non-proliferative breast changes (fibrocystic changes). (CU-03Ja)

Ans.

Morphology of non-proliferative breast changes (fibrocystic changes): There are three principal morphologic changes: a) cystic change, often with apocrine metaplasia; b) fibrosis; and c) adenosis.

1. **Cysts:** Cysts are lined either by a flattened atrophic epithelium or by metaplastic apocrine cells. Metastatic cells have an abundant granular, eosinophilic cytoplasm and round nuclei, resembling the normal apocrine epithelium of sweat glands. Calcifications are common.
2. **Fibrosis:** Cysts frequently rupture, with release of secretory material into the adjacent stroma. The resulting chronic inflammation and fibrosis contribute to palpable nodularity of the breast.
3. **Adenosis:** It is defined as an increase in the number of acini per lobule. It is a normal feature of pregnancy. In nonpregnant women, adenosis can occur as a focal change. The acini are lined by columnar epithelial cells, and calcifications are occasionally present within the lumens.

(Ref: Robbins/10th/1042)

Q. Give the morphology of fibroadenoma of breast. (RMU-22Nv, CU-20Nv)
Q. State the microscopic featres of fibroadenoma. (CU-20Ju)
Q. Short note: Fibro-adenoma of breast. (SU-12Ja, CU-16Ja,13Ju)
Q. Short note: Fibro-adenoma. (RU-18Nv)

Ans.

Fibroadenoma (adenofibroma): Fibroadenoma is the ***most common benign tumor*** of the female breast.

- **Age:** Most patients are between 15 to 30 years of age.
- **Number:** Frequently multiple and bilateral.

- **Clinical feature:** Young women usually present with a palpable mass and older women with a mammographic density or clustered calcifications. The lesion is firm, rubbery, painless, well-circumscribed and freely mobile.

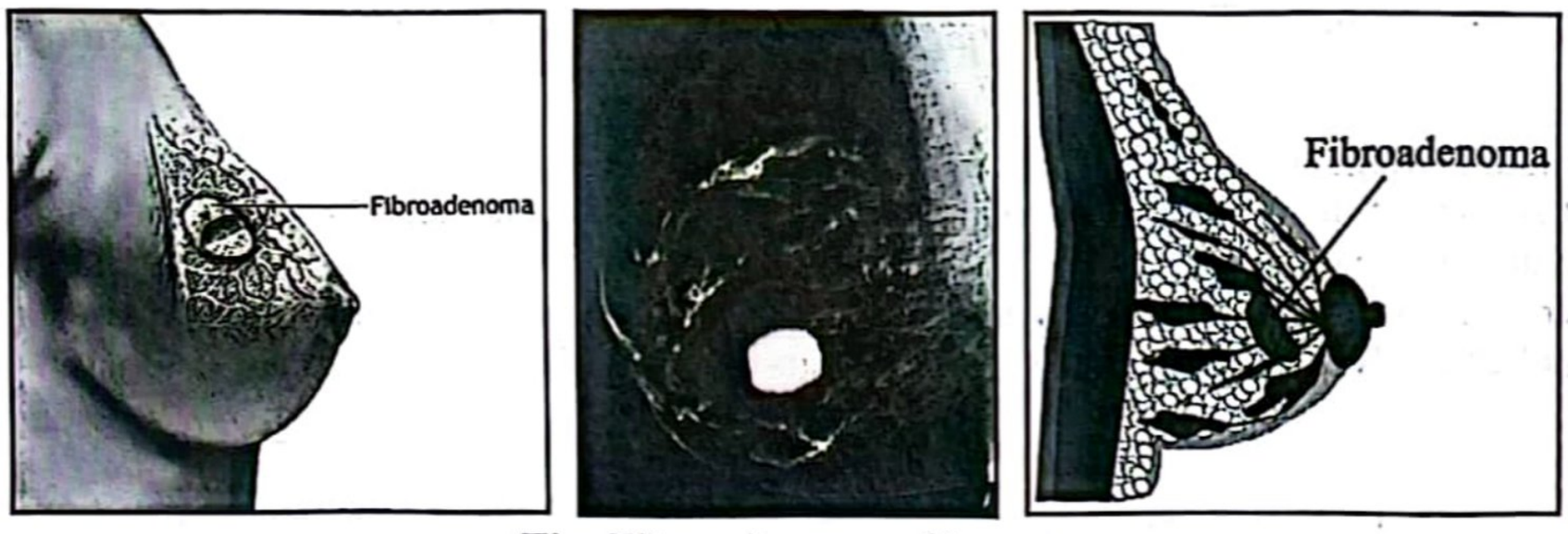


Fig: Fibroadenoma of breast.

Morphology:

***Grossly*:**

- The tumors are **well circumscribed, rubbery,** and **freely movable nodules** usually in upper-outer quadrant of breast.
- They **vary in size** from **less than 1 cm to large tumours** that replace most of the breast.
- **Cut surface** is **firm, grayish white** and often contain **slit-like spaces** (formed by compressed ducts) lined by epithelium.

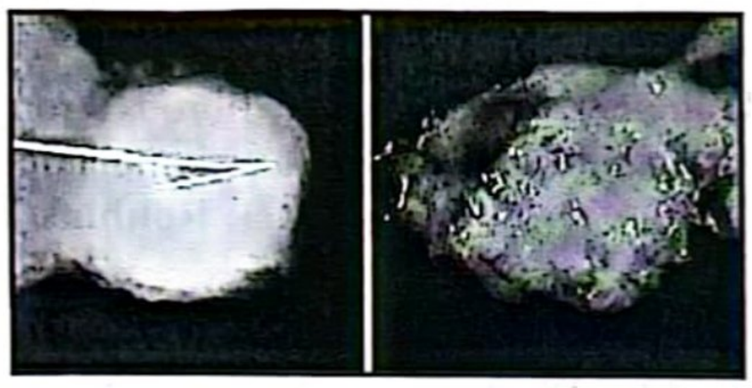


Fig: A well-circumscribed mass which is clearly demarcated from the surrounding yellow adipose tissue.

***Histologically*:**

- The stroma is usually delicate, cellular and often myxoid, resembling normal intralobular stroma.
- The arrangements between fibrous overgrowth and ducts may produce two types of patterns:
  a. **Intracanalicular pattern:** Stroma compresses and distorts ducts into ***slit-like spaces***.
  b. **Pericanalicular pattern:** Encircling masses of fibrous stroma around the ***patent or dilated ducts***.
- In older women, the stroma typically becomes densely hyalinized and the epithelium atrophic.

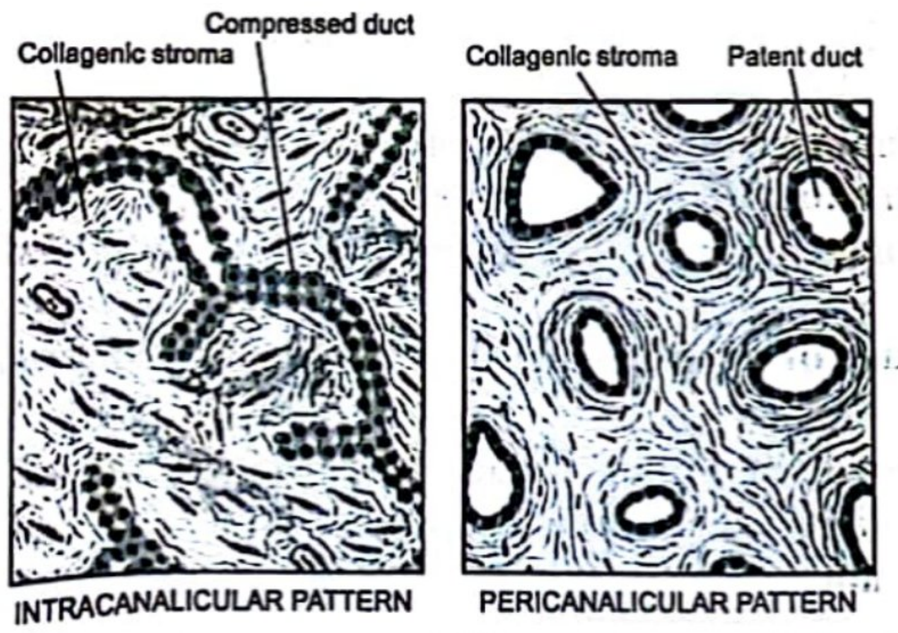
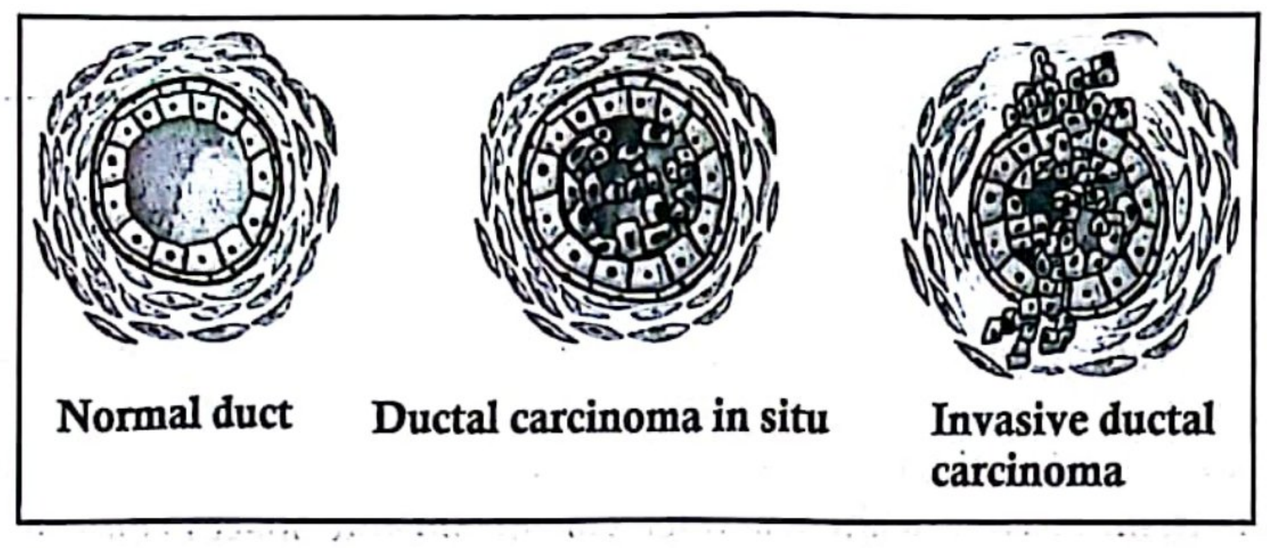


Fig: Microscopic patterns of fibroadenoma of the breast.
(Ref: Robbins/10th/1062; Harsh Mohan/7th/748; BRS Pathology/5th/311)

Q. Give the gross and microscopic features of invasive ductal carcinoma. (CU-06S)
Q. Write the morphology of invasive duct cell carcinoma of breast. (CU-16Ju)
Ans.
Morphology of invasive ductal carcinoma: Most common (70-80%) breast cancer, found more frequently in the left breast, often in the upper outer quadrant. Its precursor lesion is ***ductal carcinoma in situ***.

***Gross*:**

- Tumour is irregular, at least 2 to 3 cm in size, hard cartilage-like mass
- Cut surface of the tumour is grey-white to yellowish with chalky streaks and often extends irregularly into the surrounding fat
- There is a characteristic grating sound (similar to cutting a water chestnut) when cut or scraped.
- Less frequently, carcinomas have a well-circumscribed border and a softer consistency.



***Microscopic*:**

- Anaplastic tumour cells forming solid nests, cords, poorly-formed glandular structures and some intraductal foci.
- Infiltration by these patterns of tumour cells into diffuse fibrous stroma and fat.
- Invasion into perivascular and perineural spaces as well as lymphatic and vascular invasion.

(Ref: Robbins/10th/1055; Harsh Mohan/7th/752)

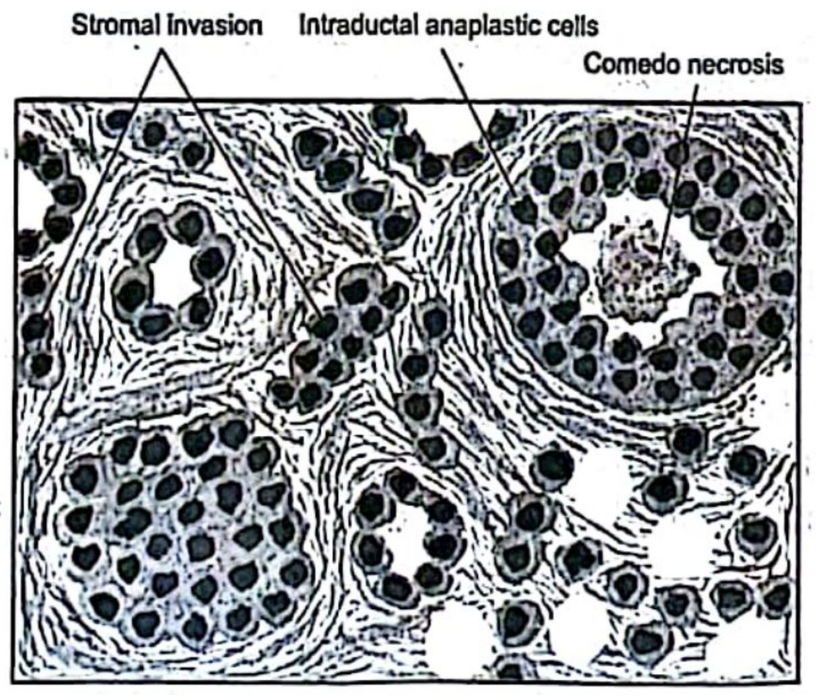


Fig: Infiltrating duct carcinoma-NOS. Microscopic features include formation of solid nests, cords, gland-like structures and intraductal growth pattern of anaplastic tumour cells. There is infiltration of densely collagenised stroma by these cells in a haphazard manner.

Q. Short note: Paget's disease of nipple. (DU-04S, CU-03S) ***(Important for VIVA)***
Ans.
Paget's disease of nipple: Paget disease of the nipple is a **rare manifestation of breast cancer** (1% to 4% of cases) that presents as a unilateral **erythematous eruption** with a **scale crust. Pruritus** is common, and the lesion may be mistaken for **eczema.**

The nipple bears a **crusted, scaly and eczematoid lesion** with a **palpable subareolar mass** in about 50-60% of cases.

It is often associated with an **invasive** or **non-invasive ductal carcinoma** of the underlying breast. Most of the patients with **palpable mass** are found to have ***invasive (infiltrating) duct carcinoma***, while those with **no palpable breast lump** are usually subsequently found to have ***intraductal carcinoma (DCIS)***.

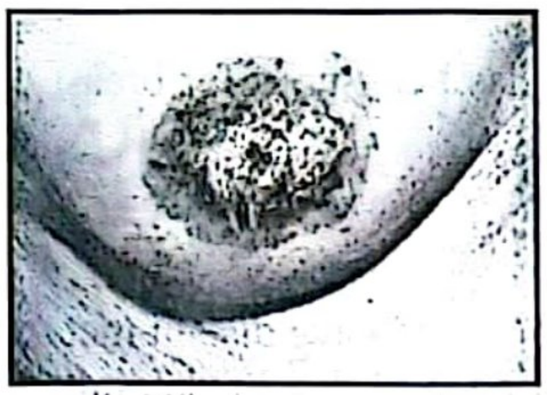


Fig: Paget's disease of nipple.

<u>Pathogenesis</u>: Malignant cells (Paget cells) extend from the underlying ductal carcinoma (DCIS) within the ductal system via the lactiferous sinuses into nipple skin without crossing the basement membrane. The malignant cells disrupt the normally tight squamous epithelial cell barrier, allowing extracellular fluid to seep out onto the nipple surface and form an oozing scaly crust.

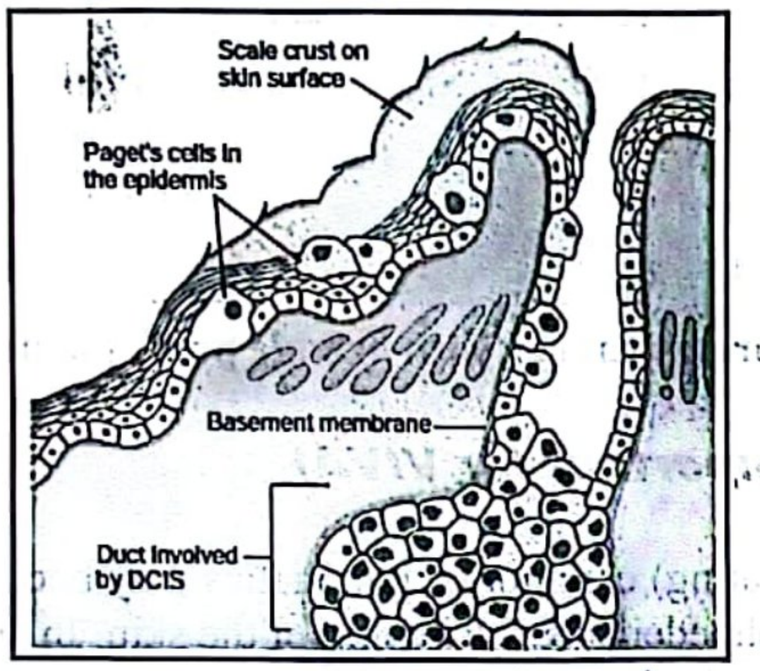


Fig: Paget disease of the nipple.

(Ductal carcinoma in situ arising within the ductal system of the breast can extend up the lactiferous ducts and into the skin of the nipple without crossing the basement membrane)

<u>Morphology</u>:

***Gross*:**

- The skin of the nipple and areola is crusted, fissured and ulcerated.
- Have oozing, hyperaemia and oedema.

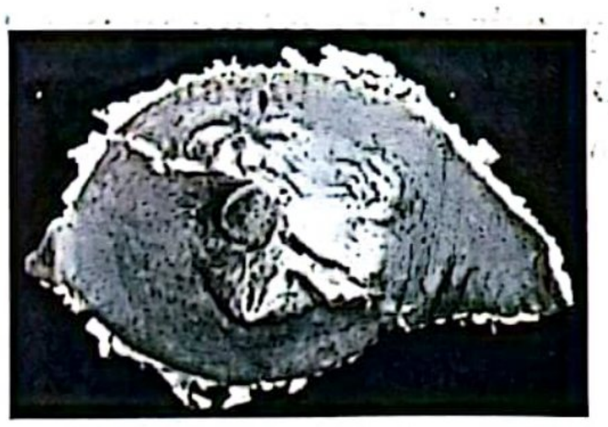


Fig: Paget's diseases of the breast. The region of nipple and areola is crusted and ulcerated.

***Microscopic*:**

- Presence of Paget's cells (malignant cells) singly or in small clusters in the epidermis.
- Paget's cells are larger than the epidermal cells, anaplastic, hyperchromatic and usually surrounded by a clear zone or halo.

<u>Diagnosis</u>:

- Nipple biopsy

- Cytologic preparation of exudate.

(Ref: Robbins/10th/1053; Harsh Mohan/7th/755; BRS Pathology/5th/312; Prof. Khaleque/134)

Q. What do you mean by inflammatory carcinoma of the breast? (RU-07Ju)

Ans.

Inflammatory breast cancer: The term has been used for breast cancers in which there is redness, oedema, tenderness and rapid enlargement.

Characteristics:

- Carcinoma of dermal lymphatics.
- Poor prognosis, as most patients prove to have distant metastases (tumor already in lymph).
- Presents as breast erythema, swelling, and skin thickening.
- The edematous skin is tethered to the breast by Cooper ligaments and mimics the surface of an **orange peel**, an appearance referred to as ***peau d'orange***.

(Ref: Robbins/10th/1058; Harsh Mohan/7th/755; Pathoma Lecture notes)

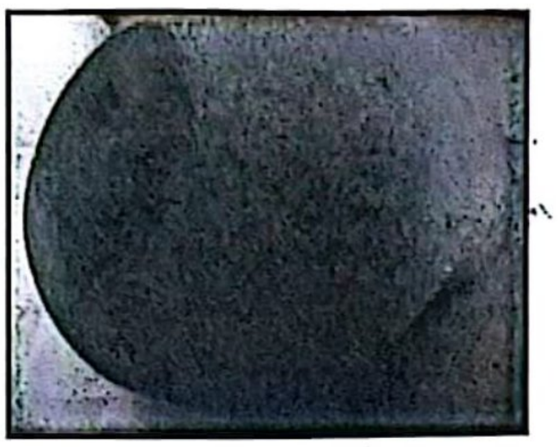


Fig: Inflammatory breast cancer with orange peel appearance (*peau d'orange*).

Q. What is peau d orange? ***(Important for VIVA)***

Ans.

Peau d orange: In invasive (infiltrating) carcinoma, lymphatics may become so involved as to block the local area of skin drainage & cause lymphoedema & thickening of the skin. In such cases edematous skin is tethered to the breast by Cooper ligaments and mimics the surface of an orange peel, an appearance referred to as *peau d'orange*.

(Ref: Robbins/10th/1058)

Q. Enumerate the causes of breast lump. (DU-08Ju,06M, RU-20Nv,17Nv/Ja,07Ju)
Q. A female of 25 years came with painless mobile breast lump. What could be the possible causes? (RMU-21Nv,11Ju)
Q. Mention causes of breast lumps in a woman aged 38 years. (RU-18Nv)
Q. Write down the differential diagnosis of breast lump in a female. (CMU-21Nv)
Q. A 38 year/20 year old female patient came to you with a lump in her left breast. Write the possible causes. (RU-19Nv,14Ju, CMU-21/17M)

Ans.

Causes of breast lump:

1. Fibrocystic disease of breast
2. Fibroadenoma of breast
3. Mastitis (acute & chronic)
4. Breast abscess
5. Fibroadenosis
6. Traumatic fat necrosis
7. Haematoma
8. Lipoma
9. Carcinoma of the breast (in situ and invasive)
10. Lymphoma involving the breast.

Nice to Know:

Clinical presentation of breast cancer (carcinoma of the breast):

(a) Presence of a painless hard lump.
(b) Breast becomes fixed and immobile, due to infiltration of suspensory ligaments.
(c) Retraction of skin, due to infiltration of suspensory ligaments.
(d) Retraction of nipple due to infiltration and fibrosis of lactiferous ducts.
(e) peau *d'orange'* appearance of the skin (i.e. skin giving rise to appearance like that of the skin of the orange) due to obstruction of superficial lymphatics.

Q. How will you proceeds to diagnosis a case of breast lump in female? (DU-06M, RU-17Nv/Ja,15Ju)
Q. How will you proceeds to diagnosis a breast lump in pathology laboratory? (CU-15Ju)
Q. How will you investigate the patient with a breast lump? (RMU-22/20M)
Q. Enumerate your approaches towards the diagnosis in case of a breast lump. (RU-07Ju)
Q. A female aged 55 years presented with lump breast and blood stained nipple discharge. Name the possible diagnosis and your way of investigating the case. (RU-10Ju)
Q. Outline the diagnosis of breast lump in the laboratory.
Q. A female of 25 years came with painless mobile breast lump. How you will investigate to establish a diagnosis? (RMU-21Nv,13Ja,11Ju)
Q. A 38 year/20 year old female patient came to you with a lump in her left breast. How will you investigate such a case? (RU-19/18Nv,14Ju, CU-17M)
Q. Short note: Breast lump and diagnosis. (RU-18Ja)

Ans.

Diagnosis of a case of breast lump:

A. History taking:

1. Age
2. Mode of presentation:
   - Mode of onset
   - Duration
   - Rate of growth
3. Pain (usually painless)
4. Discharge from nipple
5. Loss of weight
6. Personal history
7. Family history of breast and ovarian cancer

B. Examination:

1. **General examination**
2. **Local examination**

a. Inspection:

- Skin over the lump - color & texture
- Engorged vein
- Nodules
- Ulceration
- Nipple - size & shape
- Surface
- Any discharge

a. Palpation:

- Local temperature & tenderness

- Situation
- Number
- Size & shape
- Surface
- Margin
- Consistency
- Fixity to the skin
- Fixity to the breast tissue
- Fixity to the underlying fascia and muscle
- Fixity to the chest wall
- Examination of lymph nodes

C. <u>Investigations</u>:

1. Mammography
2. Ultrasonography
3. MRI scan (for high risk patients)
4. FNAC (Fine Needle Aspiration Cytology)
5. Biopsy (image guided core needle biopsy/excisional biopsy) followed by histopathology
6. Immunohistochemistry (IHC) for ER, PR & HER2 status
7. Cytological examination of nipple discharge.

Q. What do you mean by 'triple technique' in diagnosis of breast cancer? (For VIVA)

Ans.

<u>Triple technique in diagnosis of breast cancer</u>: It comprises of-

1. Palpation
2. Mammography
3. Fine needle aspiration cytology (FNAC).

(***N.B:*** Additional techniques such as stereotactic biopsy and frozen section are immensely valuable to the surgeon for immediate pathological diagnosis in doubtful cases.)

(Ref: Harsh Mohan/7th/750)

Q. A female of 23 years has presented to you with a palpable mobile lump in her left breast. The lump is well-circumscribed, mobile, and not fixed with overlying skin. What is your probable diagnosis? How will you proceed to diagnose such in the laboratory?

Ans.

<u>Probable diagnosis</u>: Fibroadenoma of breast.

<u>Investigations</u>:

- Mammography
- Ultrasonography
- FNAC (Fine Needle Aspiration Cytology) from the breast lump
- Biopsy & histopathology.

Q. A 25 years old female came to you with right breast lump. What could be the possible causes? What investigations you will perform to establish the diagnosis? (RU-13Ja)

Ans.

Possible causes:

1. Fibroadenoma
2. Fibrocystic diseases
3. Mastitis
4. Traumatic fat necrosis
5. Carcinoma of the breast

Investigations:

1. Ultrasonography of both breast and axilla
2. Bilateral diagnostic mammography
3. FNAC (Fine Needle Aspiration Cytology) from the breast lump
4. Biopsy & histopathology
5. Tumour marker: CA 15-3.

Q. A female of 55 years presented with irregular, hard, skin fixed breast lump with bloody nipple discharge. (BUP-22M)

a) **What is your provisional diagnosis?**
b) **How will you confirm the diagnosis?**

Q. A 55 years old female presented with hard fixed lump in right breast. What is your provisional diagnosis? What are the investigations need to diagnose the case? (RMU-22Nv)

Q. A 50 years old female with a hard irregular mass in the left breast. What is your probable diagnosis? How will you confirm your diagnosis? (CU-19Nv)

Q. A 50 years old woman presented with a hard breast lump, enlarging over last 2 weeks. The overlying skin shows dimpling. What is your likely diagnosis? What investigations would you perform to confirm your provisional diagnosis? (DU-13Ja)

Q. A female of 55 years has developed a breast lump for 3 months. It is firm in consistency and fixed with underlying tissue. What is the probable diagnosis? List the investigations required for the patient. (DU-11Ju)

Ans.

Diagnosis: Carcinoma breast.

Investigations:

1. Ultrasonography of both breast and axilla
2. Bilateral diagnostic mammography
3. FNAC (Fine Needle Aspiration Cytology) from the breast lump
4. Biopsy & histopathology
5. Immunohistochemistry (IHC) for ER, PR & HER2 testing.

Q. A female of 60 years has developed a hard, fixed lump in her right breast. It is gradually increased for last one month. She also noticed a swelling in right axillary region. What is the probable cause of axillary swelling and what is your diagnosis? (DU-23M)
Q. A female of 60 years old presented to you with a stony hard mass in her right breast with right sided axillary lymphadenopathy. (CMU-23M)

a) **What is your provisional diagnosis?**
b) **Name the investigations you will suggest to justify your diagnosis?**

Ans.
Probable cause of axillary swelling: Carcinoma breast with axillary lymph node metastasis.

Investigations:

1. Ultrasonography of both breast and axilla
2. Bilateral diagnostic mammography
3. USG guided core biopsy from the breast lump
4. FNAC (Fine Needle Aspiration Cytology) from the axillary lymph node
5. Immunohistochemistry (IHC) for ER, PR & HER2 testing.

Q. Write down the risk factors involved in breast cancer. (DU-08Ju, SU-20Nv, CU-20Nv) ***(V.V.I. for VIVA & MCQ)***

Ans.
Risk factors for the development of breast cancer:

1. **Gender:** 99% of affected patients are female.
2. **Age:**
   - Incidence increases with increasing age (peaking at the age of 70-80 years).
   - Rarely found before the age of 25 years except in some familial cases.
3. **Germline mutations:** Inherited mutations in the *p53, BRCA*-1, or *BRCA*-2 tumor suppressor genes are associated with increased risk.
4. **First-degree relatives with breast cancer:** First-degree relatives (mother, sister, daughter) of women with breast cancer have 2 to 6-fold higher risk of development of breast cancer.
5. **Geographic and racial factors:** Incidence of breast cancer is about 4-6 times higher in developed countries (North America, North Europe, Australia), and low in developing countries of Asia and Africa.
6. **Early menarche and late menopause (increases estrogen exposure):** Menarche at ages younger than 11 years increases risk by 20% compared to menarche at ages greater than 14. Late menopause also increases risk.
7. **Age at first pregnancy:** Nulliparity & first pregnancy after 30 years of age increases the risk.
4. **Benign breast disease:** Proliferative fibrocystic disease with atypical epithelial hyperplasia increases the risk of developing invasive carcinoma.
5. **Estrogen exposure:** Postmenopausal hormone replacement therapy (HRT) increases the risk of breast cancer, particularly when estrogen and a progestin are given together for a period of years. Oral contraceptives are unlikely to increase the risk of breast cancer.
6. **High breast density:** High breast density is potentially susceptible to neoplastic transformation. Dense breast also make detection of cancer more difficult by mammography.
7. **Radiation exposure:** Radiation of the chest, whether due to cancer therapy, atomic bomb exposure, or nuclear accidents, results in a higher rate of breast cancer.

8. **History of breast cancer in one breast:** associated with increased incidence in the opposite breast.
9. **Diet:** Large amounts of animal fats, high calorie foods; cigarette smoking, alcohol consumption increases the risk.
10. **Obesity:** Possibly due to production of estrogens by adipose tissue.
11. **Exercise:** There is a small protective effect for women who are physically active.
12. **Breast-feeding:** The longer women breast-feed, the greater is the reduction in the risk.
13. **Environmental toxins:** Environmental contaminants such as organochlorine pesticides could have estrogenic effects of humans.

(Ref: Robbins/10th/1046; BRS Pathology/5th/312; Harsh Mohan/7th/750)

Q. Outline the prognostic factors involved in breast carcinoma. (DU-23/19Nv,16/14Ju, BUP-19M, SU-08Ju)

Ans.

Prognostic factors of breast carcinoma:

A. Major prognostic factors:

1. **Invasive carcinoma versus in situ disease:**
   - In situ carcinoma is confined to the ductal system & cannot metastasize. So, great majority of DICS will be cured with adequate treatment.
   - In contrast, at least half of invasive carcinomas will have metastasized locally or distantly at the time of diagnosis. Their prognosis is bad.
2. **Distant metastases:** Once distant metastases are present, cure is unlikely.
3. **Lymph node metastases:** Axillary lymph node status is the ***most important prognostic factor*** for invasive carcinoma in the absence of distant metastasis. The less the lymph node metastasis, the more the chance of good prognosis.
4. **Tumor size:** The size of the carcinoma is the second most important prognostic factor and is independent from lymph node status. The more the size of the cancer, the prognosis is bad.
5. **Locally advanced diseases:** Carcinomas invading into skin or skeletal muscle are usually large and may be difficult to treat surgically.
6. **Inflammatory carcinoma:** Breast cancer presenting with breast swelling and skin thickening due to dermal lymphatic involvement have a particularly poor prognosis.
7. **Lymphovascular invasion:** Tumor cells are present within vascular spaces (either lymphatics or small capillaries) in about half of all invasive carcinomas. This finding is strongly associated with the presence of lymph node metastases. It is a poor prognostic factor for overall survival in women without lymph node metastases and a risk factor for local recurrence.

B. Minor prognostic factors:

1. **Molecular subtype:** The molecular subtype, determined by expression of ER and HER2 and proliferation, is an important prognostic factor.
2. **Special histologic types:** The survival rate of women with some special types of invasive carcinomas (tubular, mucinous, lobular, papillary, adenoid cystic) is greater than that of women with cancers of no special type.
3. **Histologic grade:** All invasive carcinomas are graded using the Nottingham Histologic Score that classifies invasive carcinomas into three groups (grade I, II, III) that are highly correlated with disease free and overall survival.
4. **Proliferative rate:** Tumors with high proliferation rates have a poorer prognosis but may respond better to chemotherapy.

5. **Estrogen and progesterone receptors (ER/PR):** Oestrogen is known to promote the breast cancer. Presence or absence of hormone receptors on the tumour cells can help in predicting the response of breast cancer to endocrine therapy. Accordingly, patients with high levels of ER and PR on breast tumour cells have a slightly better prognosis.
6. **HER2/neu overexpression:** HER2/neu overexpression is associated with poorer survival, but its main importance is as a predictor of response to agents that target this receptor (targeted therapy).
7. **DNA content:** Aneuploid tumors having abnormal DNA indices, have slightly worse prognosis.
8. **Response to neoadjuvant therapy:** The subgroups of patients who achieve a pathologic complete response to neoadjuvant therapy have a greater than 95% long-term survival.

(Ref: Robbins/10th/1058; Harsh Mohan/7th/755)

Q. Name the molecular subtypes of breast carcinoma. (CU-15Ju)
Q. Write down the molecular classification of breast cancer. (CU-20/19/18M)
Q. Discuss the molecular subtypes of invasive breast carcinoma. (CMU-21M,15Ju)
Ans.

Molecular classification of breast cancer: V.V.I for VIVA

1. **Luminal A:** Hormone-receptor (ER & PR) **strongly** positive; HER2 negative.
2. **Luminal B:** Hormone-receptor (ER & PR) **low** positive; HER2 negative.
3. **HER2-enriched:** HER2 **positive**; hormone-receptor (ER & PR) positive/negative.
4. **Basal-like:** Hormone-receptor (ER & PR) and HER2 **all are negative ('Triple negative')**.

Out of all these, **basal-like type** has **worst prognosis** while **luminal type A** responds well to endocrine therapy and has **good prognosis**.

(Ref: Robbins/10th/1060; BRS Pathology/5th/311; Harsh Mohan/7th/757)

Q. Discuss the role of ER, PR & HER2 in the prognosis of breast carcinoma. (DU-23Nv, CMU-21M)
Q. Discuss the role of ER & HER2 in the prognosis of breast cancer. (CU-15Ju)
Ans.

Role of ER, PR & HER2 in the prognosis of breast cancer: V.V.I for VIVA

- Tumours that express both ER & PR (or only ER or PR) is correlated with a **better prognosis**, because they **respond well to endocrine therapy**.
- Presence of HER2/neu is associated with a **poorer prognosis**, because tumours that overexpress HER2 **tend to metastasize earlier**.

(Ref: BRS Pathology/5th/312; Lecture DMC)

Q. Short note: Breast cancer. (CU-14Ja)
Ans.

Breast cancer: Carcinoma of the breast is the ***most common non-skin malignancy*** in women and is second only to lung cancer as a cause of cancer deaths. A woman who lives to age 90 has a one in eight chance of developing breast cancer.

- **Site of involvement:** Breast cancer occurs most frequently in the **upper outer quadrant** of the breast. It occurs more often in **left breast** than the right and is bilateral in about 4% cases.
- **Sites of metastasis:** Mainly in the ***axillary lymph nodes***, ***lung***, ***liver***, and ***bone***.

Risk factors for developing breast cancer: *Please write from above.*

(***N.B:*** The major risk factors for the development of breast cancer are hormonal and genetic.)

Classification of breast cancer: *Please write from above.*

The Male Breast

Q. What do you mean by gynaecomastia? (RU-07Ja)
Q. What are the causes of gynaecomastia?
Q. Short note: Gynaecomastia. (RMU-23/20M,18Nv,17Nv/Ju,14Ju) ***(Important for VIVA)***
Ans.
Gynaecomastia: Enlargement of the male breast is known as gynaecomastia.

It may be unilateral and bilateral and presents as a button-like subareolar enlargement. In advanced cases, the swelling can simulate the adolescent female breast.

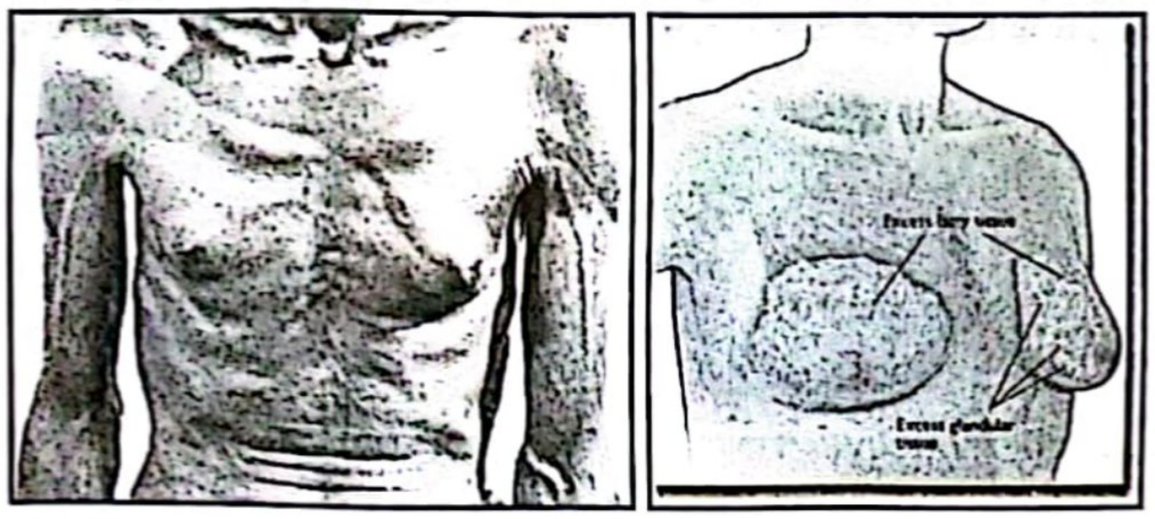


Fig: Gynaecomastia.

Pathogenesis: Gynaecomastia may occur as a result of an imbalance between estrogens, which stimulates breast tissue, and androgens, which counteract these effects.

Causes:

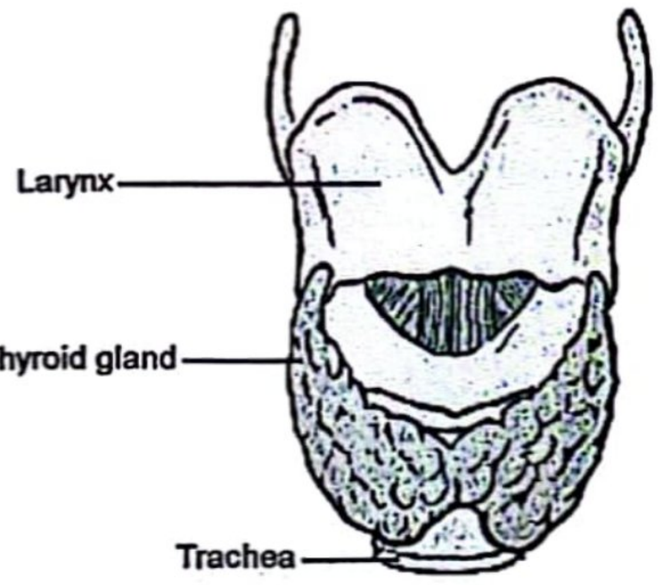
1. Pubertal gynaecomastia (young boys between 13 and 17 years of age)
2. Failure of the androgenic functions of the testis (in older males)
3. Cirrhosis of liver
4. Testicular tumours
5. Pituitary tumours
6. Carcinoma of the lung
7. Exogenous oestrogen therapy as in carcinoma of the prostate
8. Testicular atrophy in Klinefelter's syndrome (secondary gynaecomastia)
9. Drugs (such as alcohol, marijuana, heroin, antiretroviral therapy, anabolic steroids used by some athletes and body builders, and some psychoactive agents)
10. Idiopathic gynaecomastia (without any obvious cause).

(Ref: Robbins/10th/1044; Harsh Mohan/7th/748)

CHAPTER 13

ENDOCRINE SYSTEM

Thyroid Gland



Histology: The thyroid gland is divided by thin fibrous septa into **lobules** composed of **follicles** (about 20-40) which are the main functional units of the thyroid. The follicles are lined by cuboidal to low columner epithelium with numerous fine microvilli extending into the follicular **colloid** that contains the glycoprotein, ***thyroglobulin*** (which contains the ***thyroid hormones*** within its molecule). The thyroid gland follicles also contain a population of ***parafollicular cells***, or **C cells**, which synthesize and secrete the hormone ***calcitonin***.

{Ref: Robbins/10th/1075; Harsh Mohan/7th/793}

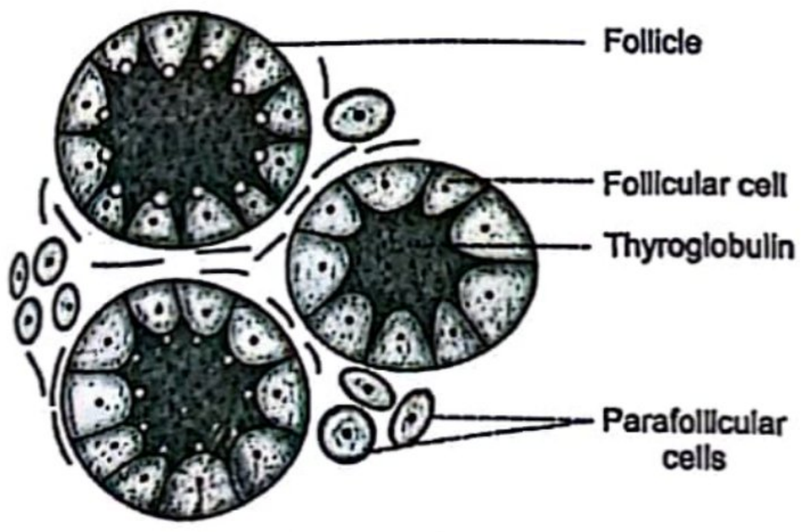


Fig: Histology of thyroid gland.

Q. Classify thyroid diseases. (CU-08Ja)
Q. Classify tumors of thyroid gland. (RMU-23M,20Nv/M, CU-20M,10Ju,09Ja, SU-12Ja,10Ju)
Q. Name the malignant tumors of thyroid gland. (SU-14Ja,09Ju)
Q. Classify thyroid tumours/neoplasms. (RMU-21Nv, SU-13Ju)
Q. Classify thyroid carcinoma. (CMU-21Nv, SU-19/18M,15Ja)
Q. Short note: Thyroid neoplasia. (RU-07Ju)

Ans.

Diseases of thyroid gland:

1. **Congenital anomalies:**
   - Thyroglossal duct
   - Thyroglossal cyst
   - Lingual thyroid
   - Median ectopic thyroid
   - Lateral aberrant thyroid

2. **Acquired diseases of thyroid gland:**
   a. **Functional disorders**
      - Hyperthyroidism *(thyrotoxicosis)*
      - Hypothyroidism – *Cretinism* (child with severe hypothyroidism), *myxedema* (adult-onset severe hypothyroidism)
   b. **Thyroiditis**
      - Hashimoto thyroiditis
      - Subacute lymphocytic (painless) thyroiditis
      - Granulomatous (de Quervain) thyroiditis
   c. **Grave's disease**
   d. **Goiter**- Diffuse nontoxic (simple) goiter, multinodular goiter
   e. **Tumors:**
      - **Benign:** Follicular adenoma.
      - **Malignant:**
        i) **Primary:**
           - Thyroid carcinoma
             - Papillary thyroid carcinoma (80-85% of cases)
             - Follicular carcinoma (10-15% of cases)
             - Anaplastic (undifferentiated) carcinoma (< 5% of cases)
             - Medullary carcinoma (5% of cases)
           - Sarcoma, lymphoma (rarely)
        ii) **Secondary:**
           - Metastatic
           - Local infiltration.

(Ref: Robbins/10th/1075-1092; Harsh Mohan/7th/793}

Nice to Know:

A number of ***thyroid function tests*** are currently available. These include the following:

- Determination of serum levels of T3, T4 by radioimmunoassay (RIA).
- TSH and TRH determination.
- Determination of calcitonin secreted by parafollicular C cells.
- Estimation of thyroglobulin secreted by thyroid follicular cells.
- Assessment of thyroid activity by its ability to uptake radioactive iodine (RAIU).
- Assessment whether thyroid lesion is a nonfunctioning ('cold nodule') or hyperactive mass ('hot nodule').

(Ref: Harsh Mohan/7th/793)

Hyper & Hypo-thyroidism

Q. Define thyrotoxicosis & hyperthyroidism. Enumerate the causes of hyperthyroidism.
Ans.
Thyrotoxicosis & hyperthyroidism: ***Hyperthyroidism***, also called ***thyrotoxicosis***, is a **hypermetabolic** clinical and biochemical state caused by ***excess production of thyroid hormones*** (T_3 and T_4).

Because it is caused most commonly by ***hyperfunction*** of the thyroid gland, it is often referred to as ***hyperthyroidism***.

(Ref: Robbins/10th/1075; Harsh Mohan/7th/793)

Causes of hyperthyroidism:

Primary:

1. Diffuse hyperplasia of the thyroid (Graves disease) - approximately 85% of cases
2. Hyperfunctioning ("toxic") multinodular goiter
3. Hyperfunctioning ("toxic") adenoma
4. Thyroiditis
5. Iodine-induced hyperthyroidism
6. Neonatal thyrotoxicosis associated with maternal Graves disease

Secondary:

1. TSH-secreting pituitary adenoma (rare).

(Ref: Robbins/10th/1076)

*{**N.B:** Strictly speaking, **hyperthyroidism is only one (albeit the most common) cause of thyrotoxicosis**, as in certain conditions the oversupply of thyroid hormone is related to either excessive release of preformed thyroid hormone (e.g. in thyroiditis) or to an extrathyroidal source (e.g. struma ovarii, exogenous thyroxine intake etc.) rather than hyperfunction of the gland.}*

(Ref: Robbins/10th/1076 + 9th/1083)

Q. Define hypothyroidism. Enumerate the causes of hypothyroidism.
Ans.
Hypothyroidism: Hypothyroidism is a **hypometabolic clinical state** resulting from **inadequate production of thyroid hormones** for prolonged periods, or rarely, from resistance of the peripheral tissues to the effects of thyroid hormones.

(Ref: Harsh Mohan/7th/793)

Or,

Hypothyroidism is a condition caused by a structural or functional derangement that interferes with the production of thyroid hormone.

(Ref: Robbins/10th/1077)

Causes of hypothyroidism:

Primary:

1. Genetic defects in thyroid development (rare)
2. Thyroid hormone resistance syndrome (rare)
3. Postablative: Surgery, radioiodine therapy, or external radiation
4. Autoimmune hypothyroidism: Hashimoto thyroiditis
5. Iodine deficiency
6. Drugs: Lithium, iodides, para-aminosalicylic acid
7. Congenital biosynthetic defect (dyshormonogenetic goiter).

Secondary (central):

1. Pituitary failure (rare)
2. Hypothalamic failure (rare).

(Ref: Robbins/10th/1077)

Nice to Know:

Clinical manifestations of hypothyroidism: *It depends upon the age at onset of disorder, and divided into 2 forms:*

1. ***Cretinism*** *or* ***congenital hypothyroidism*** *is the development of severe hypothyroidism during* ***infancy*** *and* ***childhood.***
2. ***Myxoedema*** *is the* ***adulthood*** *hypothyroidism.*

(Ref: Harsh Mohan/7th/794)

(***N.B:*** The term **myxoedema** connotes **non-pitting oedema** due to accumulation of hydrophilic ***mucopolysaccharides*** in the ground substance of dermis and other tissues.)

Q. Mention the normal values of FT_3, FT_4 & TSH.

Ans.

Normal values of FT_3, FT_4 & TSH:

- **FT_3:** 0.9 – 2.4 nmol/L (59 – 156 ng/dL)
- **FT_4:** 9 – 21 pmol/L (700 – 1632 pg/dL)
- **TSH:** 0.2 – 4.5 mU/L.

(Ref: Davidson's/21st/1295)

V.V.I. for VIVA: The measurement of **serum TSH concentration** is the **most useful / most sensitive single (number one) screening test** for **hyper/hypo-thyroidism.**

(Ref: Robbins/10th/1078)

Nice to Know:

Laboratory diagnosis / hormonal changes in hypothyroidism:

Primary hypothyroidism: *(Problem is in thyroid)*

- ***FT_3:*** *low*
- ***FT_4:*** *low*
- ***TSH:*** *elevated (>20 mU/L).*

Secondary hypothyroidism: *(Problem is in* ***pituitary****)*

- ***FT_3:*** *low*
- ***FT_4:*** *low*
- ***TSH:*** *low.*

Q. The thyroid function test of a middle aged female got high TSH and low level of T3 & T4. What is your diagnosis? What may be the causes? (RMU-22Nv)

Ans.

Diagnosis: Primary hypothyroidism.

Causes: *Please write from above.*

Thyroiditis

Q. What are the inflammatory conditions of the thyroid gland?

Ans.

Inflammatory conditions of the thyroid gland (thyroiditis): Thyroiditis encompasses a diverse group of disorders characterized by some form of ***thyroid inflammation***. This discussion focuses on the three most common and clinically significant subtypes:

- **Hashimoto thyroiditis**

- **Granulomatous (de Quervain's) thyroiditis** (painful) - probably secondary to a viral infection
- **Subacute lymphocytic** (painless) **thyroiditis** (postpartum thyroiditis).

(Ref: Robbins/10th/1178)

Q. Describe briefly the pathogenesis of Hashimoto thyroiditis. (DU-06Ja)
Q. Short note: Hashimoto thyroiditis. (DU-11Ja) ***(Important for VIVA)***
Ans.
Hashimoto thyroiditis: Hashimoto thyroiditis is an ***autoimmune disease*** that results in **destruction of the thyroid gland** and gradual and progressive **thyroid failure**.

Epidemiology: It is the most common cause of hypothyroidism in areas of the world where iodine levels are sufficient. This disorder is most prevalent between 45 and 65 years of age and is ***more common in women than in men***, with a female predominance of 10:1 to 20:1.

Pathogenesis: Hashimoto thyroiditis is caused by a ***breakdown in self-tolerance to thyroid auto-antigens*** → This results in ***progressive autoimmune destruction of thyroid cells*** by infiltrating cytotoxic T cells, locally released cytokines, or by antibody-dependent cytotoxicity.

Induction of thyroid autoimmunity is accompanied by a **progressive depletion of thyrocytes** by **apoptosis** and replacement of the thyroid parenchyma by mononuclear cell infiltration and **fibrosis**. Multiple immunologic mechanisms may contribute to thyroid cell death, including-

- **CD8+ cytotoxic T cell-mediated cell death:** CD8+ cytotoxic T cells may cause thyrocyte destruction.
- **Cytokine mediated cell death:** Excessive T-cell activation → Production of T_H1 inflammatory cytokines e.g. γ-IFN → Recruitment and activation of macrophages → Damage to follicles.
- **Binding of anti-thyroid antibodies** (***anti-thyroglobulin***, and ***anti-thyroid peroxidase*** antibodies) followed by antibody dependent cell-mediated cytotoxicity.

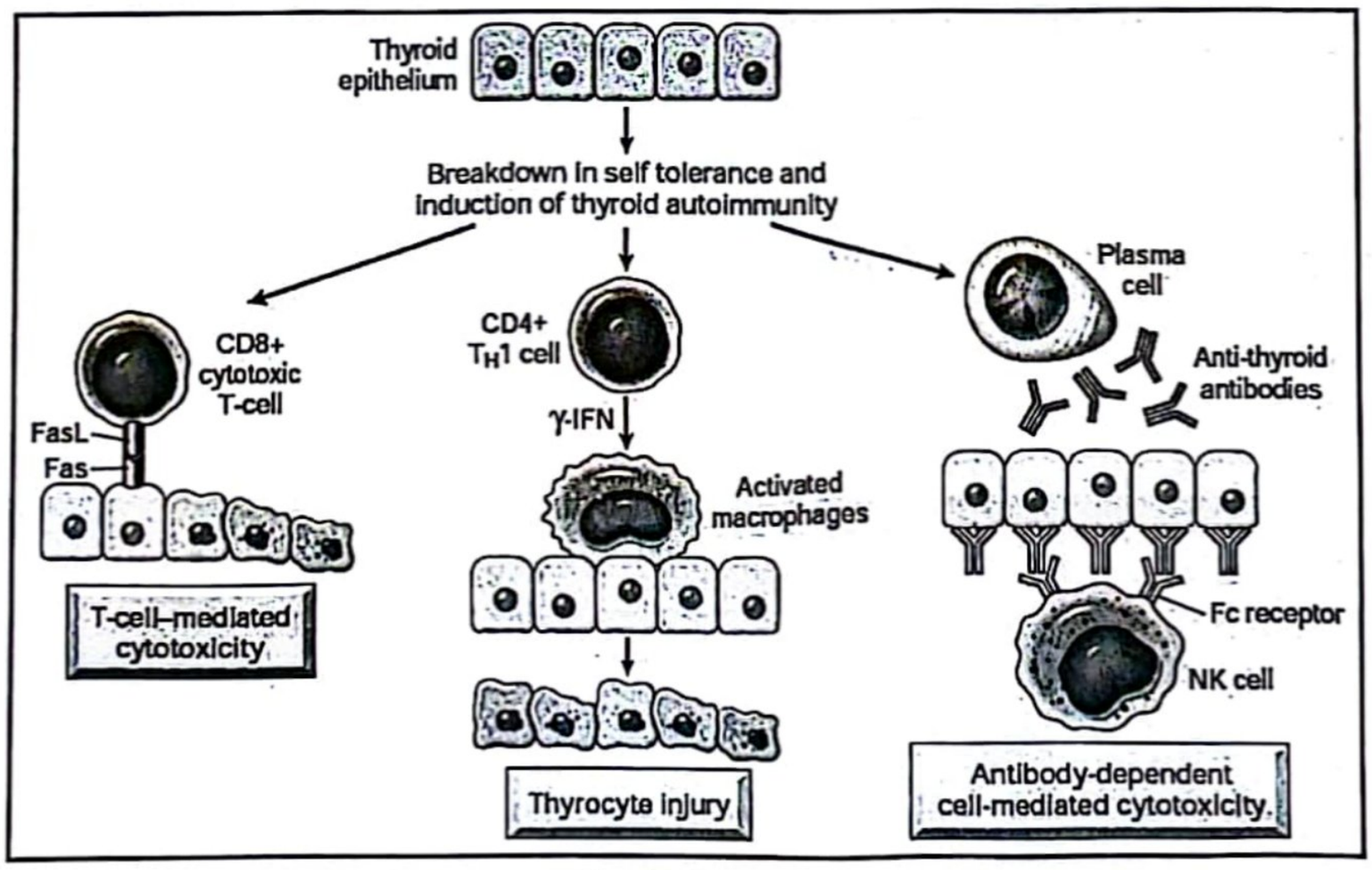


Fig: Pathogenesis of Hashimoto thyroiditis.

Morphology:

Grossly:
- Thyroid gland is usually diffusely enlarged.
- The capsule is intact, and the gland is well demarcated from adjacent structures.
- Cut surface is pale, yellow-tan, firm, and somewhat nodular.

Microscopically:
- Extensive infiltration of the parenchyma by a **mononuclear inflammatory infiltrate** containing small lymphocytes, plasma cells, and well developed **germinal centres.**

- The thyroid follicles are atrophic and are lined in many areas by epithelial cells distinguished by presence of abundant eosinophili, granular cytoplasm, termed **Hürthle cells.**
- Presence of Hürthle cells in conjunction with a heterogenous population of lymphocytes is characteristics of Hashimoto thyroiditis.

(Ref: Robbins/10th/1078)

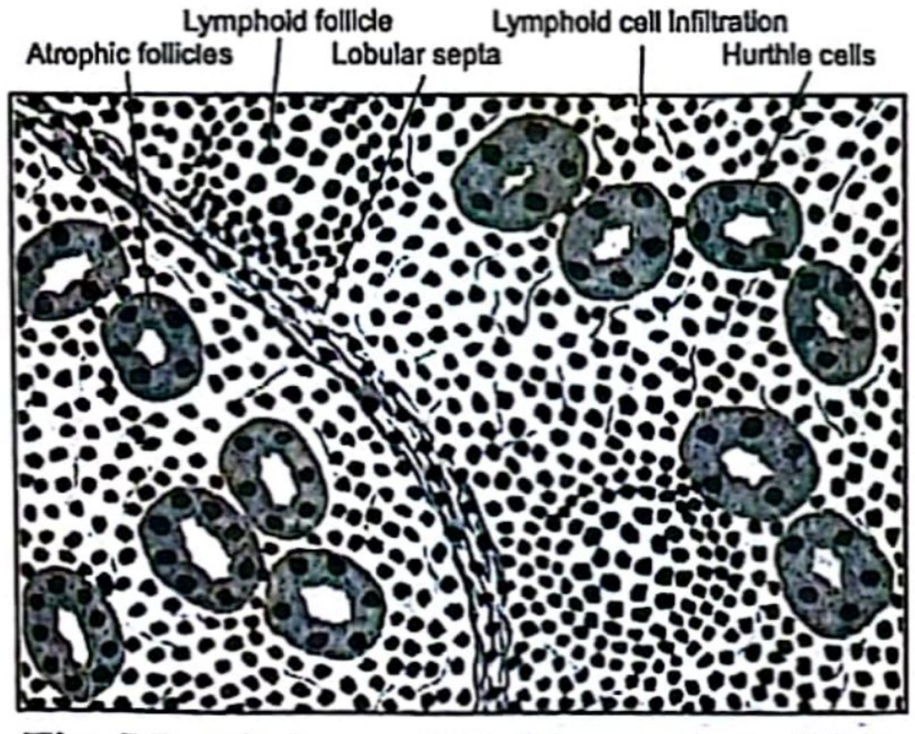


Fig: Morphology of Hashimoto thyroiditis.

Grave's Disease

Q. Mention the expected laboratory findings in Grave's disease.
Q. Short note: Grave's disease. (BUP-22Nv,16Ja, DU-19M,15/14/10/08Ju) ***(Important for VIVA)***

Ans.

Grave's disease: Grave's disease is an ***autoimmune thyroid disorder*** which the **most common** cause of endogenous ***hyperthyroidism*** and is characterized by a **triad** of clinical findings-

1. ***Hyperthyroidism*** associated with **diffuse enlargement of the thyroid gland**
2. Infiltrative ***ophthalmopathy*** with resultant ***exophthalmos***
3. Localized, infiltrative ***dermopathy*** (sometimes called ***pretibial myxedema***).

Age: It has a peak incidence between 20 & 40 years of age. Women are affected as much as 10 times more frequently than men.

Pathogenesis: Grave's disease is an ***auto-immune disease,*** caused by the production of ***multiple autoantibodies*** against the ***TSH receptor***. These are as under:

- Thyroid-stimulating immunoglobulin (TSI) - stimulates increased release of thyroid hormone.
- Thyroid growth stimulating immunoglobulins (TGI) - stimulates proliferation of follicular epithelium.
- TSH-binding inhibitor immunoglobulins (TBII) - inhibitory to binding of TSH to its own receptor.

Depending upon its action as inhibitory or stimulatory to follicular epithelium, it may result in alternate episodes of **hypo-** and **hyperthyroidism**.

Morphology:

***Macroscopically*:**

- Symmetrical enlargement of thyroid gland due to diffuse hypertrophy and hyperplasia of thyroid follicular epithelial cells.
- Increase in weight to over 80 gm.
- On cut section, the parenchyma has a soft, meaty appearance resembling normal muscle.

***Microscopically*:**

- The follicles are small and are lined by tall columnar epithelium and more crowded than usual.
- There is considerable epithelial hyperplasia and hypertrophy and formation of papillary infoldings of piled up epithelium into the lumina of follicles.
- The colloid is markedly diminished.
- The stroma shows increased vascularity and accumulation of lymphoid cells; germinal centers are common.

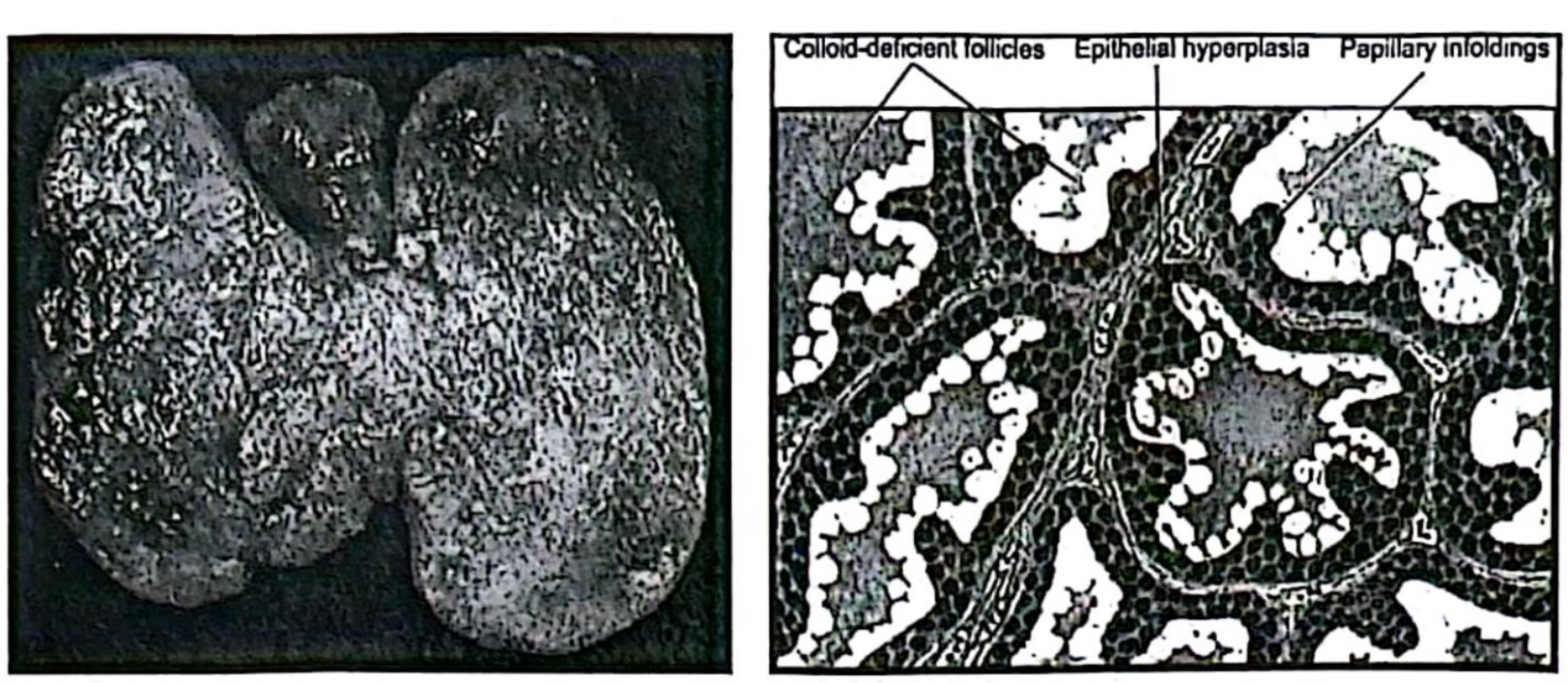


Fig: Morphology of Graves' disease.

Clinical features: *(Important for VIVA)*

1. Diffuse enlargement of the thyroid (diffuse goiter) with features of thyrotoxicosis
2. Ophthalmopathy (exophthalmos)
3. Dermopathy (scaly thickening and induration of the skin overlying the shins - pretibial myxedema)

Laboratory findings: *(Important for VIVA)*

- **Serum TSH level: ↓**
- **Serum free T_3 and T_4 level: ↑**
- **Radioactive iodine uptake (RAIU):** Very high.
- **Thyroid scanning:** Diffuse uptake of iodine throughout the gland.
- **Thyroid auto-antibody:** TSH receptor antibody / thyroid receptor antibody (TRAb).

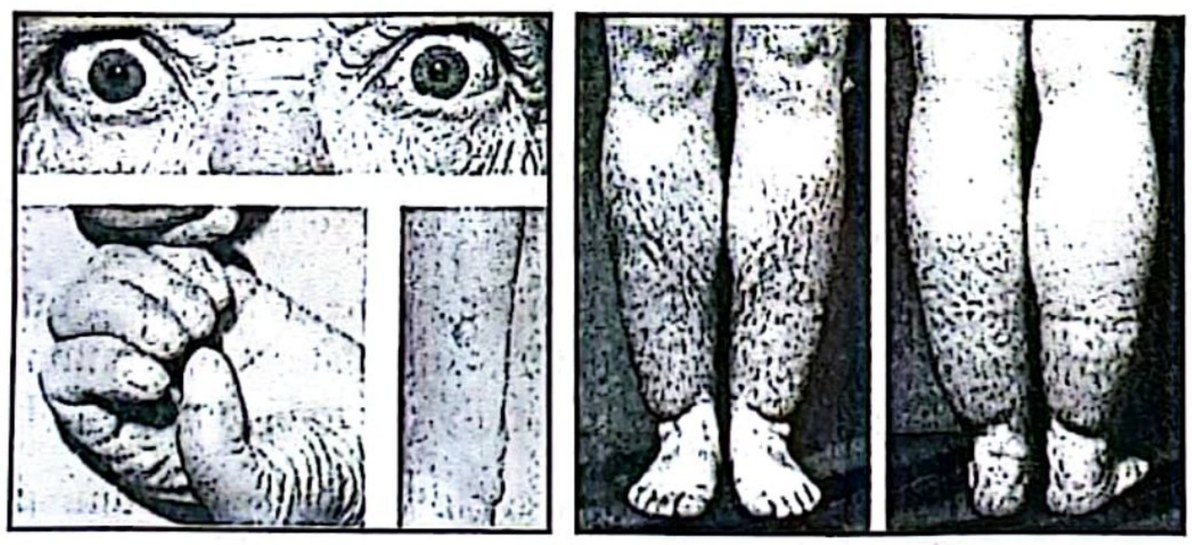


Fig: Clinical features of Grave's disease.

Treatment: *(Important for VIVA)*

- Anti-thyroid drugs (carbimazole or propylthiouracil)
- β-blocker (propranolol) – reduces sympathetic symptoms such as tremor, tachycardia, palpitation, sweating, and anxiety).
- Radioiodine therapy
- Surgery (subtotal thyroidectomy).

(Ref: Robbins/10th/1081; Harsh Mohan/7th/797)

Nice to Know:

In **Graves ophthalmopathy**, the protrusion of the eyeball (exopthalmos) is caused by an increase in the volume of the retro-orbital connective tissues and extraocular muscles, which occurs for several reasons:

1. Marked infiltration of connective tissue by mononuclear cells, predominantly T cells
2. Inflammation, edema, and swelling of extraocular muscles
3. Accumulation of extracellular matrix components, specifically hydrophilic glycosaminoglycans such as hyaluronic acid and chondroitin sulfate
4. Increased numbers of adipocytes (fatty infiltration).

These changes not only displace the eyeball but also may interfere with the function of the extraocular muscles.

(Ref: Robbins/10th/1081)

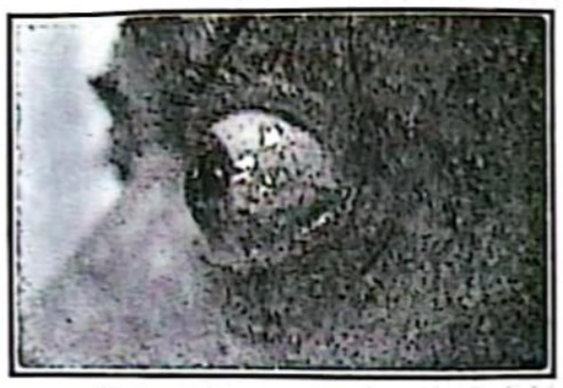


Fig: Exopthalmos.

Q. A 30 years old lady presented with diffuse enlargement of thyroid gland with exopthalmous. What is your clinical diagnosis? What will be the status of thyroid hormone level in this case? (DU-13Ju)

Ans.

Clinical diagnosis: Grave's disease.

Status of thyroid hormone level:

1. ↓ Plasma TSH
2. ↑ Plasma FT_4
3. ↑ Plasma FT_3.

Q. A 30 year old lady presented with diffuse enlargement of thyroid gland, exopthalmos and high serum free T_3 and T_4 level. What is your diagnosis? What immunological mechanisms contribute to its development? (DU-12Ja)

Ans.

Diagnosis: Grave's disease.

Immunological mechanism: It is an ***autoimmune disease*** in which circulating ***antibodies*** are formed ***against the TSH receptor*** and ***activates the receptor making the thyroid gland hyperactive***.

Goiter

Q. What is goiter? (DU-17Nv,07Ju,06Ja, CU-19Nv) **Classify goiter.**

Q. Short note: Goiter. (CU-20M)

Ans.

Goiter: The term **'goitre'** means **any enlargement of the thyroid gland**, which is caused by compensatory hyperplasia and hypertrophy of the follicular epithelium in response to thyroid hormone deficiency.

Pathogenesis: Impairment of thyroid hormone synthesis leads to a compensatory rise in the serum TSH level, which, in turn, causes hypertrophy and hyperplasia of thyroid follicular cells and, ultimately, gross enlargement of the thyroid gland (goiter).

Types of goiter:

1. **Diffuse non-toxic (simple) goiter**
   - Endemic goiter
   - Non-endemic / Sporadic goiter
2. **Multinodular goiter**
   - Toxic multinodular goiter
   - Non-toxic multinodular goiter.

(Ref: Robbins/10th/1082; Harsh Mohan/7th/797)

Q. What are the causes of goiter? (DU-18M,17Nv)

Ans.

Causes of goiter:

1. Physiological
   - Puberty
   - Pregnancy
2. Autoimmune disorder: Graves' disease (over active goiter)
3. Hashimoto thyroiditis (under active goiter)
4. Iodine deficiency goiter (endemic) – occurs in geographic areas in which the diet is deficient in iodine.
5. Goitrogens (Foods or drugs that suppress synthesis of thyroid hormones)
6. Tumours (very rare)
   - Benign
   - Malignant
7. Congenital (maternal anti-thyroid drugs, maternal hyperthyroidism, dyshormonogenesis).

(Ref: BRS Pathology/5th/322; Robbins/10th/1082)

Q. What is simple goiter? Describe its pathogenesis (CU-20Nv,04Ja) **& causes.**

Q. Short note: Diffuse non-toxic goiter.

Ans.

Simple goiter (colloid goiter): Diffuse non-toxic (simple) goiter specifies a form of goiter that causes enlargement of the entire gland without producing nodularity.

Because the **enlarged follicles are filled with colloid**, the term **colloid goiter** has been applied to this condition.

(Ref: Robbins/10th/1083)

Pathogenesis:

Lack of iodine (i.e. dietary iodine deficiency)
↓
↓ Synthesis of thyroid hormone
↓
Compensatory rise in the serum TSH level
↓
Hypertrophy and hyperplasia of the thyroid follicular cells
↓
Gross enlargement of the thyroid gland.

Fig: A patient of simple goiter.

(Ref: Robbins/10th/1083)

Types and causes:

a. **Endemic goiter:** Goiter occurring with high frequency in ***iodine-deficient geographic areas***.
   - Occurs in geographic areas where the soil, water, and food supply contain only low levels of iodine. Such conditions are particularly common in mountainous areas of the world, where iodine deficiency is widespread.

b. **Sporadic goiter:** Goiter occurring in ***non-iodine-deficient areas***.
   - There is a striking female preponderance and a peak incidence at puberty or in young adult life.
   - Ingestion of ***goitrogenic substances*** that interfere with thyroid hormone synthesis, such as excessive calcium and vegetables belonging to the Brassicaceae (Cruciferae) family (e.g. cabbage, cauliflower, Brussels sprouts, turnips, and cassava).
   - Hereditary ***enzymatic defects*** that interfere with thyroid hormone synthesis.
   - In most cases, however, the cause of sporadic goiter is not apparent.

(Ref: Robbins/10th/1083; BRS Pathology/5th/323)

Nice to Know:
- **Goitrogens:** Foods or drugs that suppress synthesis of thyroid hormones, such as excessive calcium and vegetables belonging to the Brassicaceae (Cruciferae) family (e.g. cabbage, cauliflower, Brussels sprouts, turnips, and cassava etc.).
- **Endemic goiter:** The term endemic is used when goiters are present in more than 10% of the population in a given region.

(Ref: Robbins/10th/1083)

Q. What is multinodular goiter? Give the etiopathogenesis of multinodular goiter. (DU-18M)
Q. Write the pathogenesis of nodular / multinodular goiter. (CMU-23M,19Nv)
Q. Write the morphological features of nodular goiter. (CMU-21Nv)
Q. Write the microscopic features of nodular goiter of thyroid. (CU-16Ja)
Q. Short note: Multinodular goiter. (SU-11Ju)

Ans.

Multinodular goiter: Irregular enlargement of the thyroid, resulting in **nodule formation**, termed as **multinodular goiter**. Virtually all long-standing simpler goiters convert into multinodular goiters.

(Ref: Robbins/10th/1083; BRS Pathology/5th/323)

Epidemiology:
- They occur in both endemic & sporadic forms (as they derived from simple goiter).
- More common in female.
- Affect older individuals because they are late complications.

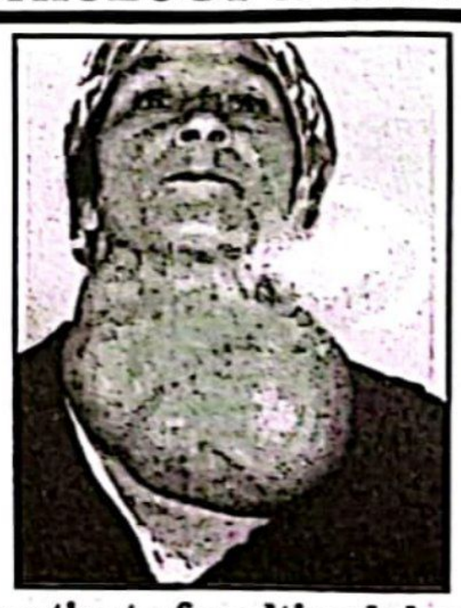


Fig: A patient of multinodular goiter.

Types:

1. Non-toxic multinodular goiter.
2. Toxic multinodular goiter.

Causes of multinodular goiter: Virtually all long standing simple goiter convert into multinodular goiters. So, they have same origins, but affecting older individuals because they are late complications.

Pathogenesis: Dietary I_2 deficiency → ↓T_3 & T_4 production by thyroid gland → ↓blood T_3 & T_4 → ↑TSH secretion from anterior pituitary → persistent TSH stimulation of thyroid gland → uneven follicular hyperplasia → generation of new follicles & uneven accumulation of colloids → ↑tension & stress in the thyroid gland causing rupture of follicles and vessels → hemorrhage, cystic change, scarring & sometimes calcification → scarring adds tension → in this cyclic manner nodularity appears.

Morphology:

***Grossly*:**

- Multilobulated, asymmetrically enlarged glands that can achieve a weight of more than 2000 gm.
- The enlargement may involve one lobe far more than the other, producing lateral pressures on midline structures, such as the trachea and esophagus.
- In other instances, the goiter grows behind the sternum and clavicles to produce the so-called **intra-thoracic** or **plunging goiter.**
- Occasionally, most of it is hidden behind the trachea and esophagus.
- On cut section, irregular nodules containing variable amounts of brown, gelatinous colloid.
- Older lesions have areas of hemorrhage, fibrosis, calcification, and cystic change.

***Histologically*:**

- Colloid-rich follicles lined by flattened, inactive epithelium.
- Areas of follicular hyperplasia, accompanied by the degenerative changes.

(Ref: Robbins/10th/1083)

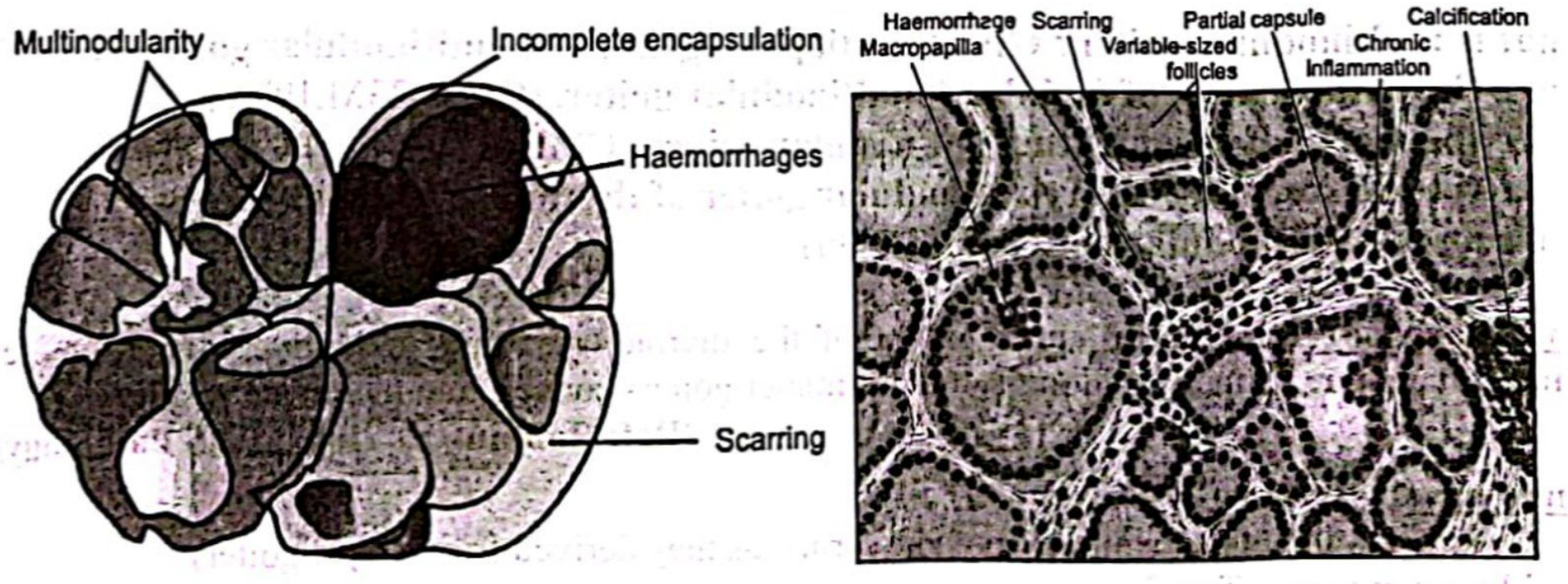


Fig: Morphology of nodular goiter.

Super Important to Know:

- ***Non-toxic goiter:*** *Goiter without thyroid hormone dysfunction.*
- ***Toxic goiter:*** *Goiter associated with hyperthyroidism.*

*(**N.B:** If the patient is euthyroid or hypothyroid, the term non-toxic goiter is appropriate.)*

Thyroid Carcinoma

Thyroid malignancies:

1. **Primary:**
   - Thyroid carcinoma
     - Papillary carcinoma (80-85% of cases)
     - Follicular carcinoma (10-15% of cases)
     - Anaplastic (undifferentiated) carcinoma (< 5% of cases)
     - Medullary carcinoma (5% of cases)
   - Lymphoma and sarcoma (rarely)
2. **Secondary:**
   - Metastatic
   - Local infiltration.

{Ref: Robbins/10th/1084-1092; Harsh Mohan/7th/793}

Q. Enumerate in short about the pathogenesis of thyroid cancer. (CU-08Ja)

Ans.

Pathogenesis of thyroid cancer:

1. **Genetic factors:** Distinct genetic events are involved in the pathogenesis of the four major histologic variants of thyroid cancer.
   - **Papillary carcinomas:** Activation of the MAP kinase pathway by rearrangement of the tyrosine kinase receptors RET or NTRK (neurotrophic tyrosine kinase receptor), and point mutations in the BRAF.
   - **Follicular carcinomas:** Mutations in the RAS family of oncogenes.
   - **Anaplastic (undifferentiated) carcinomas:** Inactivating point mutations in the p53 tumor suppressor genes.
   - **Medullary thyroid carcinomas:** Multiple endocrine neoplasia type 2 (MEN-2) and RET protooncogenes mutations.
2. **Environmental factors:** Exposure to ionizing radiation, particularly during the 1st 2 decades of life.

(Ref: Robbins/10th/1094)

Q. What are the premalignant tumors of thyroid gland? (CU-04S)

Ans.

Premalignant tumors of thyroid gland:

- Solitary thyroid nodule (cold nodule)
- Thyroid cyst
- Follicular adenoma
- Hashimoto's thyroiditis
- Carcinoid tumor of thyroid
- C-cell hyperplasia.

Nice to Know:

Several criteria provide clues to the nature of a thyroid nodule:

- *Solitary nodules, nodules in younger patients, and nodules in males* are more likely to be **neoplastic.**
- A history of *radiation treatment* to the head and neck region is associated with an increased incidence of **thyroid malignancy.**
- Functional nodules that take up radioactive iodine in imaging studies *(hot nodules)* are much more likely to be **benign.**

(Ref: Robbins/10th/1085)

Q. Discuss the morphologic features of papillary carcinoma of thyroid. (SU-22/19M,14Ja, 13Ju,12Ja,10/ 09Ju, CU-08Ja)

Q. Write the microscopic features of papillary carcinoma of thyroid gland. (DU-17Nv, CU-18Nv/M,16Ju)

Q. Write the histological findings of papillary carcinoma. (DU-15Ja, CU-09Ja)

Q. Mention the histological features of classical papillary thyroid carcinoma. (CU-19M)

Q. Short note: Papillary carcinoma of thyroid. (DU-12/04Ja, SUST-21Nv/M, BUP-20Nv/M, RU-19M)

Ans.

Papillary carcinoma of thyroid:

- Most common form of thyroid cancer (80-85%).
- They occur throughout life but most often between the ages of 25 and 50.
- Found in about three times more frequently in females than in males.
- Account for the majority of thyroid carcinomas associated with previous exposure to ionizing radiation.

Morphology:

***Grossly*:**

- Solitary or multi focal lesions within the thyroid.
- Some tumors are well circumscribed & even encapsulated; others may infiltrate the adjacent parenchyma with ill-defined margins.
- The lesions may contain areas of fibrosis and calcification and are often cystic.
- Cut surface sometimes reveals **papillary foci** that point to the diagnosis.

***Microscopically*:**

- **Branching papillae** having a fibrovascular stalk covered by a single to multiple layers of cuboidal epithelial cells.
- **Nuclei** of the papillary carcinoma cells are **optically clear** or **empty** appearance (**Ground-glass** or **Orphan Annie eye** nuclei).
- Concentrically **calcified structures** termed **psammoma bodies** are often present within the lesion, usually within the cores of the papillae.

*(**N.B:** The **diagnosis of papillary carcinoma** can be made based on these **nuclear features,** even in the absence of papillary architecture.)*

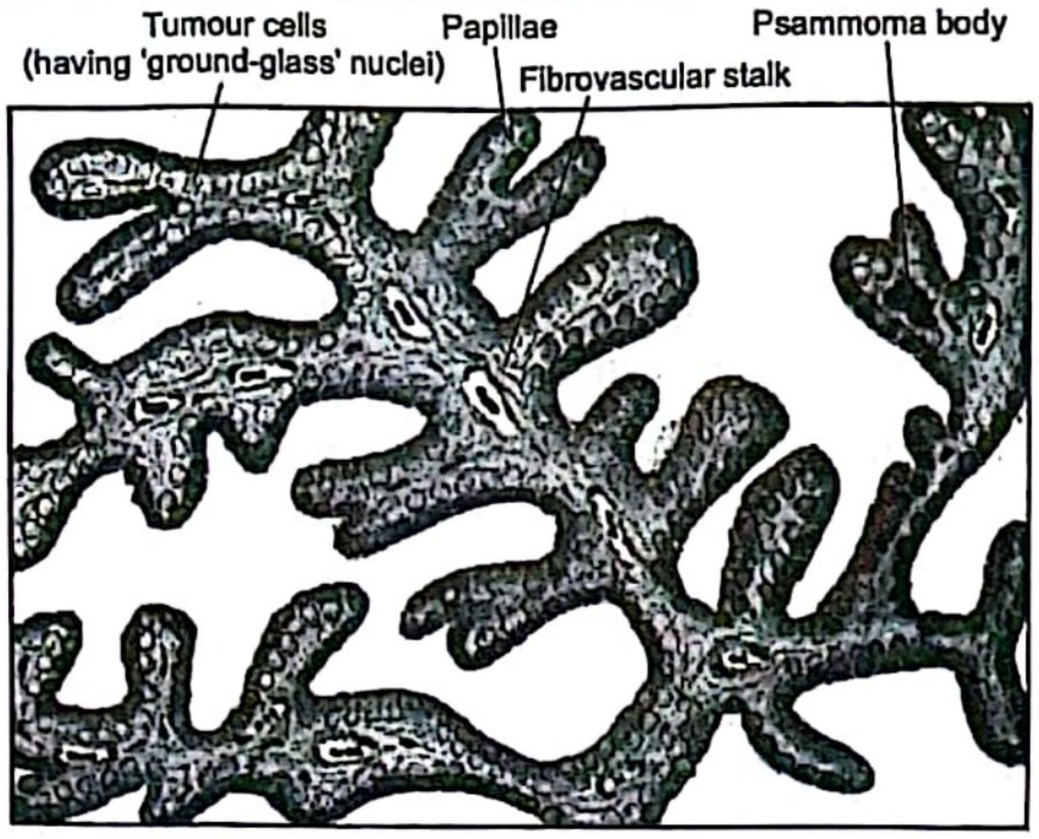


Fig: Morphology of papillary carcinoma thyroid.

Clinical features:

- Asymptomatic thyroid nodule
- Cervical lymphadenopathy (regional lymph node metastasis)
- The nodule moves freely during swallowing
- Hoarseness, dysphagia, cough, or dyspnea suggests advanced disease
- **Distant metastasis is rare** (in a minority of patients, hematogenous metastasis may occur, most commonly in the lung).

Investigation:

- Radionuclide scanning test
- Neck ultrasound with FNAC (fine-needle aspiration cytology)
- Scintiscans.

Metastases: Metastases to adjacent cervical lymph node is common but distant metastases to organs are rare.

Prognosis: Excellent, with a **10 year survival** rate in excess of 95%. ***(Very Important for VIVA)***

(Ref: Robbins/10th/1088; Harsh Mohan/7th/802)

Q. Give the histological features / morphology of follicular carcinoma of thyroid. (SU-18M,15Ju, CU-06M)

Q. Short note: Follicular carcinoma of thyroid.

Ans.

Follicular carcinoma: Follicular carcinomas are the **second most common** form of thyroid cancer, accounting for 10-15% of all thyroid cancers.

Incidence: They are common in women (3:1) and present at an older age than do papillary carcinomas, with a pick incidence between 40 and 60 years of age.

Morphology:

***Grossly*:**

- Follicular carcinomas are single nodules that may be well-circumscribed or widely infiltrative.
- Larger lesions may penetrate the capsule and infiltrate well beyond the thyroid capsule into the adjacent neck.
- They are gray to tan to pink on cut section.
- Degenerative changes, such as central fibrosis, and foci of calcification, are sometimes present.

Microscopically:

- Most follicular carcinomas are composed of fairly uniform cells forming **follicles of various sizes** containing **colloid**.
- Occasional tumors are dominated by cells with abundant granular, eosinophilic cytoplasm **(Hürthle cells)**.
- **Vascular invasion** and **direct extension** to involve the adjacent structures (e.g. **into the capsule)** are significant features but lymphatic invasion is rare.

(***N.B:*** The tumour differs from papillary carcinoma in lacking: papillae, ground-glass nuclei of tumour cells and psammoma bodies.)

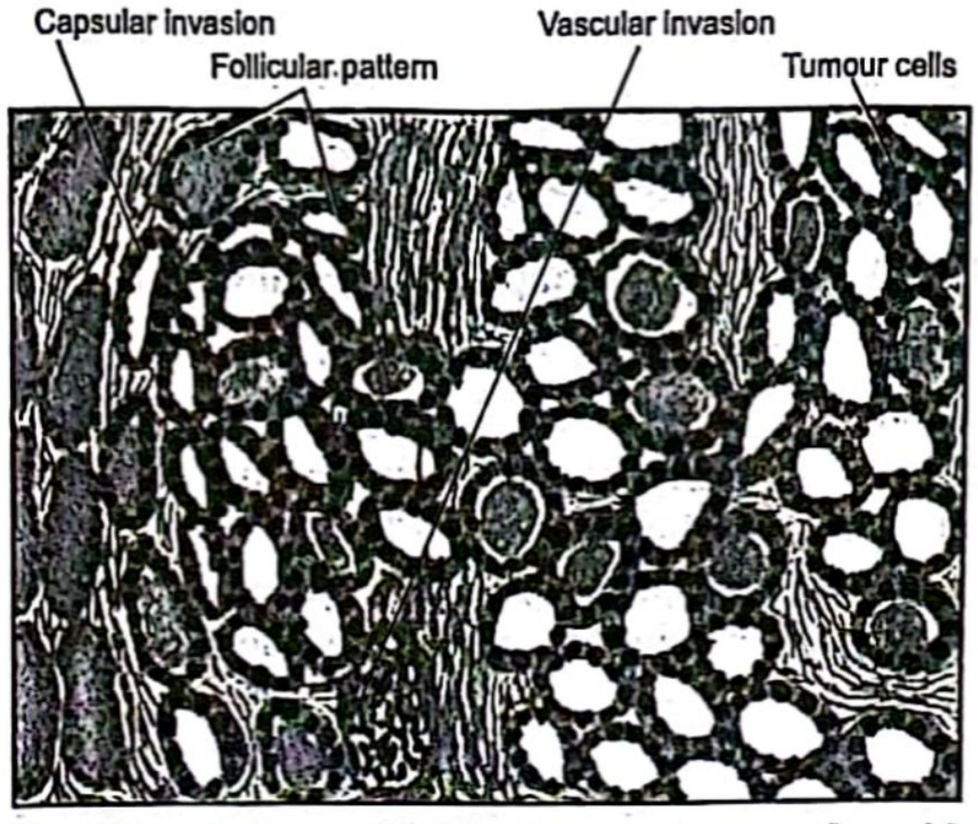


Fig: Morphology of follicular carcinoma thyroid.

Metastasis: Regional lymph node metastases are rare but distant metastases by haematogenous route are common, especially to the bones, lungs & liver.

Prognosis: Largely dependent on the extent of invasion and stage at presentation. 10 year overall survival is 50-70%.

Treatment: Most follicular carcinomas are treated with total thyroidectomy followed by the administration of radioactive iodine. Thyroid hormone is also given after surgery to suppress endogenous TSH.

(Ref: Robbins/10th/1089; Harsh Mohan/7th/803)

Q. How will you differentiate papillary carcinoma of thyroid from follicular carcinoma? (DU-07Ju)

Ans.

Differences between papillary carcinoma of thyroid and follicular carcinoma:

Traits	Papillary carcinoma	Follicular carcinoma
2. Frequency	Most common (80-85%)	10-15%
3. Peak age group	25-50 years	40-60 years
4. Cause	Previous exposure to ionizing radiation	Dietary iodine deficiency
5. Genetic alterations	RET / NTRK1 gene overexpression	RAS mutation
6. On scintiscan	Cold	Warm
7. Pathognomonic microscopy	▪ Nuclear features (ground-glass or Orphan Annie eye nuclei) ▪ Papillary pattern ▪ Psammoma bodies	Vascular and capsular invasion
8. Regional metastases	Common	Rare

9. Distant metastases	Rare	Common
10. Route of metastases	Lymphatic	Vascular
11. 10-year survival	80-95%	50-70%

(Ref: Robbins/10th/1086-1089; Harsh Mohan/7th/802)

Q. Write down the contrasting features of different types of thyroid carcinoma. (CMU-22M)

Ans.

Contrasting features of different types of thyroid carcinoma:

	FEATURE	PAPILLARY CARCINOMA	FOLLICULAR CARCINOMA	MEDULLARY CARCINOMA	ANAPLASTIC CARCINOMA
1.	*Frequency*	75-80%	10-20%	5%	5%
2.	*Age*	All ages	Middle to old age	Middle to old age; familial too	Old age.
3.	*Female/male ratio*	3:1	2.5:1	1:1	1.5:1
4.	*Relation to radiation*	Maximum	Present	None	Present
5.	*Genetic alterations*	*RET* gene over-expression, *NTRK* gene rearrangement	*RAS* mutation, *PAX-PPAR γ1* fusion	*RET* point mutation	*p53* loss, β-catenin mutation
6.	*Cell of origin*	Follicular	Follicular	Parafollicular	Follicular
7.	*Gross*	Small, multifocal	Moderate size, nodular	Moderate size	Invasive growth
8.	*Pathognomonic microscopy*	Nuclear features, papillary pattern	Vascular and capsular invasion	Solid nests, amyloid stroma	Undifferentiated, spindle-shaped, giant cells
9.	*Regional metastases*	Common	Rare	Common	Common
10.	*Distant metastases*	Rare	Common	Rare	Common
11.	*10-year survival*	80-95%	50-70%	60-70%	5-10% (median survival about 2 months)

(Ref: Harsh Mohan/7th/802)

Q. Enumerate in short about the prognosis of thyroid cancer. (CU-08Ja)

Ans.

Prognosis of thyroid cancer: The prognosis largely depends on several factors including age, extent of invasion and stage at presentation (presence or absence of distant metastasis).

- **Papillary carcinoma:** Excellent prognosis, with a 10-year overall survival rate in excess of 95%. 5-20% of patients have local or regional recurrence, and 10-15% have distant metastases.
- **Follicular carcinoma:** 10-year overall survival rate 50-70%.
- **Medullary carcinoma:** Pognosis is excellent if no metastases. It has a late metastases and spread by lymphatics and blood. 10-year overall survival rate 60-70%.
- **Anaplastic carcinoma:** There is no effective therapy for anaplastic thyroid carcinoma, and the disease is almost uniformly fatal. Although metastases to distant sites are common, in most cases death occurs in less than one year as a result of aggressive growth and compromise of vital structures in the neck. 10-year overall survival rate 5-10% and median survival about 2 months.

(Ref: Robbins/10th/1086-1092; Harsh Mohan/7th/802)

Q. A 25 years lady presented with a solitary nodule in the right lobe of thyroid gland with right sided cervical lymphadenopathy for three months. (BUP-21Nv/M)

a) What is your probable diagnosis?

b) What investigations will you carry out to confirm the diagnosis?

Ans.

Probable diagnosis: Carcinoma thyroid.

Investigations to confirm the diagnosis:

1. Serum TSH, FT3 & FT4
2. Thyroid scan
3. USG of thyroid including the neck
4. FNAC or biopsy from the thyroid nodule
5. Lobectomy followed by histopathology.

The Endocrine Pancreas

The endocrine pancreas consists of about 1 million clusters of cells, the ***islets of Langerhans,*** which contain **four major** and **two minor cell types**. The four main types are β, α, δ, and PP (pancreatic polypeptide) cells. They can be differentiated by the ultrastructural characteristics of their granules, and by their hormone content.

- The ***β cells*** produce insulin, which regulates glucose utilization in tissues and reduces blood glucose levels, as will be detailed in the discussion of diabetes.
- The ***α cells*** secrete glucagon, which stimulates glycogenolysis in the liver and thus increases blood sugar.
- The ***δ cells*** secrete somatostatin, which suppresses both insulin and glucagon release.
- The ***PP cells*** secrete pancreatic polypeptide, which exerts several gastrointestinal effects, such as stimulation of secretion of gastric and intestinal enzymes and inhibition of intestinal motility. These cells not only are present in islets but also are scattered throughout the exocrine pancreas.

There are also two rare cell types, *D1 cells* and *enterochromaffin cells*.

- ***D1 cells*** elaborate vasoactive intestinal polypeptide (VIP), a hormone that induces glycogenolysis and hyperglycemia; it also stimulates gastrointestinal fluid secretion and causes secretory diarrhea.
- ***Enterochromaffin cells*** synthesize serotonin and are the source of pancreatic tumors that cause the carcinoid syndrome.

(Ref: Robbins/10th/1097)

Q. Name the diseases of the endocrine pancreas.

Ans.

Diseases of the endocrine pancreas:

A. Diabetes mellitus

B. Islet cell tumors / pancreatic neuroendocrine tumors / PanNETs

- β-cell tumors (insulinomas)
- Zollinger-Ellison syndrome (Gastrinoma)
- MEN

C. Other rare pancreatic endocrine neoplasms

- α-cell tumors (glucagonomas)
- δ-cell tumors (somatostatinomas)
- VIPoma
- Pancreatic carcinoid tumors
- Pancreatic polypeptide-secreting endocrine tumors

- Multi-hormonal tumors (pancreatic and extrapancreatic) – produce insulin, glucagon, gastrin, ACTH, MSH, ADH, serotonin, and norepinephrine etc.

(Ref: Robbins/10th/1097-1115)

Q. What is pancreatitis?

Q. What is acute pancreatitis? Write down the causes of acute pancreatitis.

Ans.

Pancreatitis: Pancreatitis is inflammation in the pancreas associated with injury to the exocrine parenchyma.

Acute pancreatitis: Acute pancreatitis is reversible pancreatic parenchymal injury associated with inflammation.

Causes of acute pancreatitis:

Common causes:

- Biliary tract disease (Gallstones)
- Alcoholism

***Less common causes*:**

1. **Obstruction of the pancreatic duct system:**
   - Peri ampullary neoplasms (Pancreatic cancer
   - Pancreas divisum
   - Choledochoceles
   - Biliary sludge
   - Parasites *(Ascaris lumbricoides* and *Clonorchis sinensis)*
2. **Medications:**
   - Furosemide
   - Azathioprine
   - Estrogens
3. **Infections:** Mumps
4. **Metabolic disorders:**
   - Hypertriglyceridaemia
   - Hyperparathyroidism
   - Hypercalcemic states
5. **Ischemic injury from:**
   - Shock
   - Vascular thrombosis
   - Embolism
   - Vasculitis
6. **Trauma:**
   - Blunt abdominal trauma
   - Iatrogenic injury: During surgery or Endoscopic retrograde cholangio pancreatography (ERCP)
7. **Inherited alterations in genes encoding pancreatic enzymes and their inhibitors.**

(Ref: Robbin's/8th/893)

Clinical features of acute pancreatitis:

1. **Abdominal pain**
   - Constant and intense
   - Referred to the upper back and left shoulder
   - Severity: Mild & uncomfortable to severe & incapacitating
2. **Anorexia, nausea, vomiting**
3. **Full blown acute pancreatitis:** A medical emergency; results in

- Leukocytosis
- Hemolysis
- DIC
- Fluid sequestration
- Acute respiratory distress syndrome (ARDS)
- Peripheral vascular collapse and shock
- Acute tubular necrosis.

(Ref: Robbin's/8th/895,896)

Q. What are the sequelae of acute pancreatitis?

Ans.

Sequelae of acute pancreatitis:

1. Systemic organ failure
   - Shock
   - ARDS
   - Acute renal failure
2. DIC
3. Pancreatic abscess
4. Pancreatic pseudocyst
5. Duodenal obstruction.

(Ref: Robbin's/8th/896)

Q. What is chronic pancreatitis? Mention the causes of chronic pancreatitis.

Ans.

Chronic pancreatitis: Chronic pancreatitis is defined as the inflammation of the pancreas with irreversible destruction of exocrine parenchyma, fibrosis and in the late stages, the destruction of the endocrine parenchyma.

Causes of chronic pancreatitis:

1. Long term alcohol abuse (most common cause)
2. Long standing obstruction of the pancreatic duct by-
   - Pseudocysts
   - Calculi
   - Trauma
   - Neoplasms
   - Pancreas divisum
3. Tropical pancreatitis
4. Hereditary pancreatitis.

(Ref: Robbin's/8th/896)

Q. What are the sequelae of chronic pancreatitis?

Ans.

Sequelae of chronic pancreatitis:

1. Pseudocyst
2. Duct obstruction
3. Malabsorption, steatorrhoea
4. Secondary diabetes.

(Ref: Robbin's/8th/898)

Diabetes Mellitus (DM)

Q. Define (DU-17Nv,08Ju, RU-20/18Nv, CU-05Ja) **and classify diabetes mellitus.** (DU-17Nv, RU-18Nv)

Q. What are the different types of diabetes mellitus? (DU-18Nv,17M)

Ans.

Diabetes mellitus (DM): Diabetes mellitus is a clinical syndrome characterised by an increase in plasma blood glucose (**hyperglycaemia**) due to **absolute** or **relative deficiency of insulin.**

(Ref: Davidson's/23rd/722)

Or,

Diabetes mellitus is a group of **metabolic disorders** sharing the common feature of **hyperglycemia** caused by defects in **insulin secretion, insulin action,** or, mostcommonly, **both.**

(Ref: Robbins/10th/1097)

Classification of DM:

A. Type 1 diabetes (T1D) *(β-cell destruction, usually leading to absolute insulin deficiency)*
- Immune-mediated
- Idiopathic (autoantibody-negative)

B. Type 2 diabetes (T2D) *(combination of insulin resistance and β-cell dysfunction)*

C. Other types:

1. Genetic defects of β-cell function
- Maturity-onset diabetes of the young (MODY)
- Neonatal diabetes
- Maternally inherited diabetes and deafness (MIDD)
- Defects in proinsulin conversion
- Insulin gene mutations

2. Genetic defects in insulin action
- Type A insulin resistance
- Lipoatrophic diabetes

3. Exocrine pancreatic defects ("pancreatogenic" or type 3C diabetes)
- Pancreatitis
- Pancreatectomy/ trauma
- Pancreatic cancer
- Cystic fibrosis
- Haemochromatosis
- Fibrocalculous pancreatopathy

4. Endocrinopathies:
- Acromegaly
- Cushing syndrome
- Hyperthyroidism
- Pheochromocytoma
- Glucagonoma

5. Infections:
- Cytomegalovirus
- Coxsackie B virus
- Congenital rubella

6. Drugs:
- Glucocorticoids
- Thyroid hormone
- Interferon-α
- Protease inhibitors
- β-adrenergic agonists
- Thiazides
- Nicotinic acid
- Phenytoin (dilantin)
- Vacor

7. **Genetic syndromes associated with diabetes:**
   - Down syndrome
   - Kleinfelter syndrome
   - Turner syndrome
   - Prader-Willi syndrome
8. **Gestational diabetes mellitus.**

(Ref: Robbin's/10th/1099; Davidson's/23rd/733)

Q. What do you mean by type 1 diabetes mellitus? Give its etiology and pathogenesis.
Q. Write down the pathogenesis of type 1 diabetes mellitus.
Q. Short note: Type 1 diabetes mellitus.

Ans.

Type 1 diabetes (T1D) / Insulin-dependant DM (IDDM) / Juvenile onset DM: *Type 1 diabetes (T1D)* is an autoimmune disease characterized by pancreatic β cell destruction and an absolute deficiency of insulin.

It accounts for approximately 5% to 10% of diabetes and is the most common subtype diagnosed in patients younger than 20 years of age.

Pathogenesis of type 1 diabetes mellitus: Type 1 diabetes is generally considered a **T-cell-mediated autoimmune disease** involving **destruction of the insulin-secreting β cells** in the pancreatic islets.

As in all autoimmune diseases, genetic susceptibility and environmental factors play important roles in the pathogenesis.

- **Autoimmunity:** Chronic autoimmune attack on β-cells contributes to β-cell destruction. The mechanisms of β-cell destruction are-
  a. Infiltration of the islets with mononuclear cells containing activated macrophages, CD4+ T helper cells, CD8+ cytotoxic T cells, NK cells & B lymphocytes. This lesion is called insulitis.
  b. Locally produced cytokines such as IFN-γ, produced by T cells, and TNF and IL-1, produced by macrophages damage β-cells.
  c. Autoantibodies against islets cells and insulin are produced in 70-80% of patients.
- **Genetic susceptibility:** HLA-DR3 and DR4 are associated with increased susceptibility to type 1 diabetes.
- **Environmental factors:** Viruses such as coxsackieviruses group B, mumps, measles, cytomegalovirus, rubella, and infectious mononucleosis.

(Ref: Robbin's/10th/1099,1101; Davidson's/23rd/728)

Q. Write down the pathogenesis of diabetes mellitus. (DU-04M)
Q. Write down the pathogenesis of type 2 diabetes mellitus.

Ans.

Type 2 diabetes / Non-insulin-dependant DM (NIDDM) / Adult onset DM: *Type 2 diabetes* is caused by a combination of peripheral resistance to insulin action and an inadequate secretory response by the pancreatic β cells **("relative insulin deficiency")**.

Approximately 90% to 95% of diabetic patients have type 2 diabetes, and the vast majority of such individuals are overweight.

Etiopathogenesis of type 2 diabetes mellitus:

***Etiology*:**

1. Genetic factors
2. Obesity
3. Sedentary life style
4. Dietary habit (overeating, especially when combined with obesity and under-activity)
5. Age - Middle aged and elderly (usually above 40 years).

***Pathogenesis*:** Development of T2D involves two key abnormalities-

1. **Insulin resistance:** Decreased response of peripheral tissues, especially skeletal muscle, adipose tissue, and liver, to insulin.
2. **β-cell dysfunction:** Inadequate insulin secretion in the face of insulin resistance and hyperglycemia

(Ref: Robbin's/10th/1103; Davidson's/23rd/730)

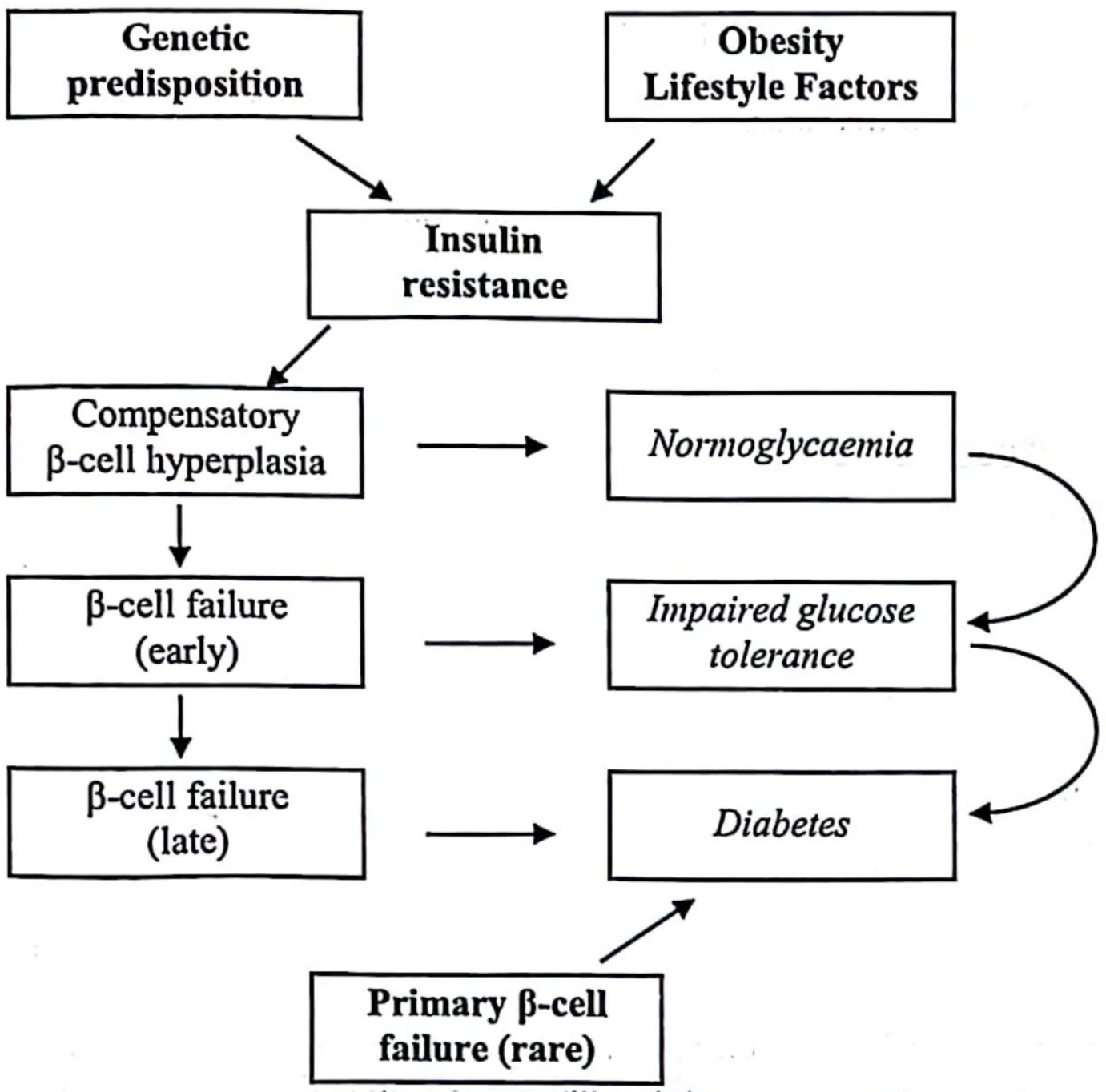


Fig: Metabolic staging of type 2 diabetes mellitus.

(***N.B*:** The combination of obesity, hyperglycemia, increased serum cholesterol and triglycerides, and hypertension is called the ***metabolic syndrome***.)

(Ref: Robbin's/10th/1103)

Nice to Know:

Type 1 diabetes was previously termed **"insulin-dependant DM" (IDDM)** and is invariably associated with profound insulin deficiency requiring replacement therapy.

Type 2 diabetes was previously termed **"non-insulin-dependant DM" (NIDDM)** because patients retain the capacity to secrete some insulin but exhibit impaired sensitivity to insulin (insulin resistance) and can usually be treated without insulin replacement therapy.

However, upto 20% of patients of type 2 diabetes will ultimately develop profound insulin deficiency requiring replacement therapy so that IDDM and NIDDM are misnomers.

(Ref: Davidson's/23rd/728)

Q. Mention the differences between type 1 and type 2 diabetes mellitus. (DU-18M, CMU-23M, BUP-18M)

Q. Write down 5 differences between type 1 and type 2 diabetes mellitus. (BUP-22M)

Q. What are the characteristics of type 1 diabetes mellitus? (DU-22Nv)

Ans.

Differences between type 1 and type 2 diabetes mellitus:

Traits	Type 1 DM	Type 2 DM
1. Typical age at onset	< 40 years	> 50 years
2. Duration of symptoms	Weeks	Months to years
3. Body weight	Normal or low	Obese
4. Ketonuria	Yes	No
5. Rapid death without treatment with insulin	Yes	No
6. Autoantibodies	Positive in 80–90%	Negative
7. Diabetic complications at diagnosis	No	25%
8. Family history of diabetes	Uncommon	Common
9. Other autoimmune disease	Common	Uncommon

(Ref: Davidson's/23rd/735)

Q. Mention the clinical features of diabetes mellitus.

Ans.

Clinical features of diabetes mellitus:

A. ***Classic triad of diabetes*:**

1. Polyuria
2. Polydipsia
3. Ployphagia

B. ***Others*:**

1. Ketoacidosis
2. Dehydration
3. Muscle wasting
4. Weakness
5. Weight loss.

(Ref: Robbin's/10th/1106)

{***N.B*:** The clinical manifestations of diabetic ketoacidosis include fatigue, nausea and vomiting, severe abdominal pain, a characteristic fruity odor, and deep, labored breathing (also known as ***Kussmaul breathing***)}.

(Ref: Robbin's/10th/1106)

Q. What are the complications of diabetes mellitus? (DU-21Ja,20Nv/M,19/18Nv,17Nv/M,12Ju, RMU-21Nv,20M,18Nv,09Ju)

Q. Write briefly about the macrovascular and microvascular complications of diabetes mellitus? (DU-18M)

Q. Short note: Complications of diabetes mellitus. (RU-17M,16Ju)

Ans.

Complications of diabetes mellitus:

Acute complications:

1. Diabetes ketoacidosis
2. Hypoglycaemic coma
3. Hyperglycaemic hyperosmolar state (HHS)
4. Lactic acidosis

Chronic complications:

A) ***Microvascular / neuropathic:***

1. **Diabetic retinopathy**
   - Impaired vision
2. **Diabetic nephropathy**
   - Renal failure

3. **Diabetic neuropathy**
   - Sensory loss
   - Motor weakness
   - Pain
4. **Autonomic neuropathy**
   - Gastrointestinal problems (gastroparesis; altered bowel habit)
   - Postural hypotension
5. **Diabetic foot disease**
   - Ulceration
   - Arthropathy

B) ***Macrovascular:***

1. **Coronary circulation**
   - Myocardial ischaemia / infarction
2. **Cerebral circulation**
   - Transient ischaemic attack
   - Stroke
3. **Peripheral circulation**
   - Claudication
   - Ischemia (e.g. gangrene of the lower extremities).

(Ref: Davidson's/23rd/734,756; Robbin's/10th/1106,1107)

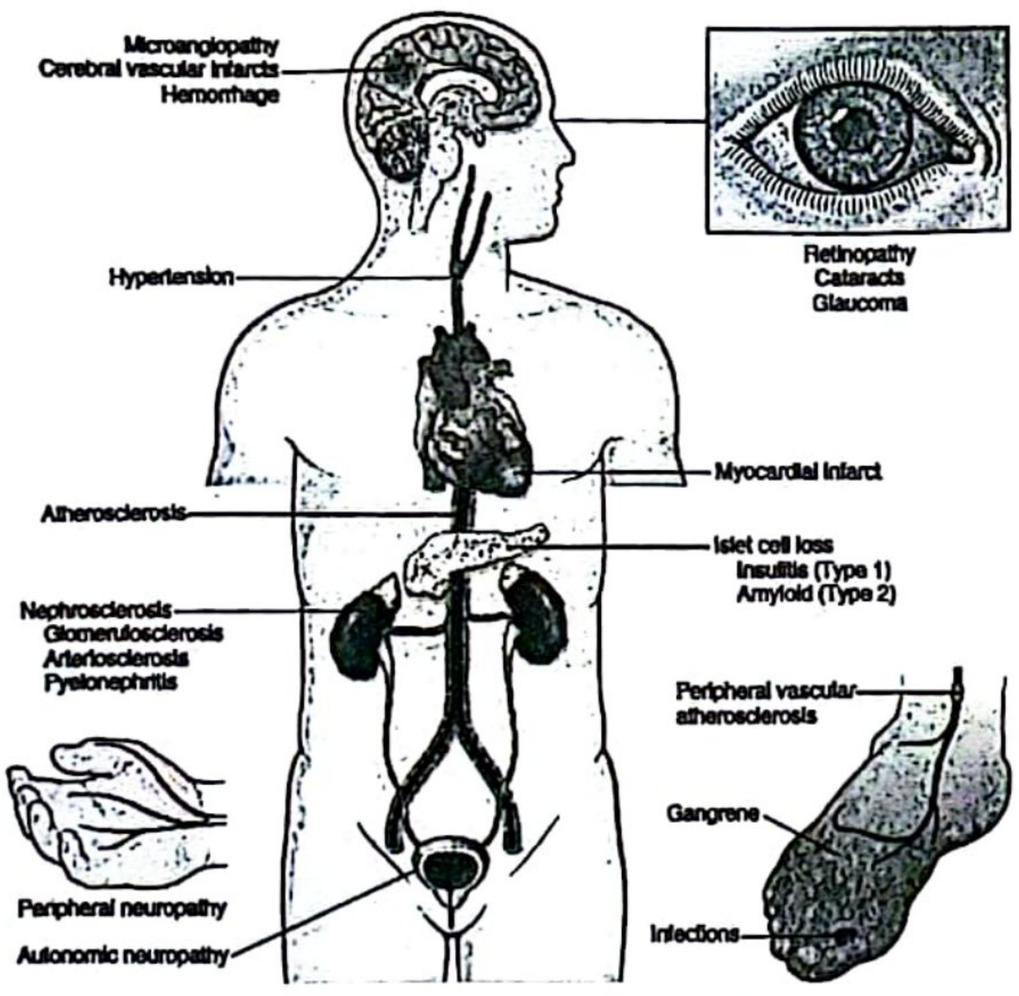


Fig: Long-term complications of diabetes.

Nice to Know:

Hypoglycaemia: Causes of hypoglycaemia include missing a meal, excessive physical exertion, excessive insulin administration, or "misdosing" during the phase of dose finding for antidiabetic agents such as sulfonylureas.

The **signs and symptoms** of hypoglycemia include dizziness, confusion, sweating, palpitations, and tachycardia; if hypoglycemia persists, loss of consciousness may occur.

Rapid reversal of hypoglycemia through oral or intravenous glucose intake is critical for preventing permanent neurologic damage.

(Ref: Robbin's/10th/1106; Davidson's/23rd/739)

Q. Mention the causes of death in diabetes mellitus.

Ans.

Causes of death in diabetes mellitus:

1. Myocardial infarction (most common cause of death in diabetes)
2. Renal failure
3. Cerebrovascular accidents.

(Ref: Robbin's/10th/1109)

Q. Describe the effects of diabetes mellitus on kidney.

Ans.

Effects of diabetes mellitus on kidney: The kidneys are prime targets of diabetes. Renal failure is second only to MI as a cause of death from this disease. **Three** lesions are encountered:

1. **Glomerular lesions:**
   - Capillary basement membrane thickening
   - Diffuse mesangial sclerosis
   - Nodular glomerulosclerosis
2. **Renal vascular lesions, principally atherosclerosis.**
3. **Pyelonephritis, including necrotizing papillitis.**

(Ref: Robbin's/10th/1110)

CHAPTER 14

THE SKIN

Normal structure of skin: Normal skin is composed of 2 layers - the epidermis and the dermis. The lining epithelium of skin is ***keratinized stratified squamous epithelium***.

EPIDERMIS: The epidermis is composed of the following **5 layers** from base to the surface:

1. Stratum basalis (stratum germinatum) } Basal layer
2. Stratum spinosum
3. Stratum granulosum
4. Stratum lucidum (present exclusively in palms and soles)
5. Stratum corneum (superficial layer containing dead keratinocyte, devoid of nuclei).

The epidermis contains 4 types of cells:

1. Squamous epithelial cells (keratinocytes)
2. Melanocytes (responsible for the production of melanin)
3. Langerhans cells (intraepidermal dendritic cells) (bone marrow-derived cells of mononuclear-phagocytic system).
4. Merkel cells.

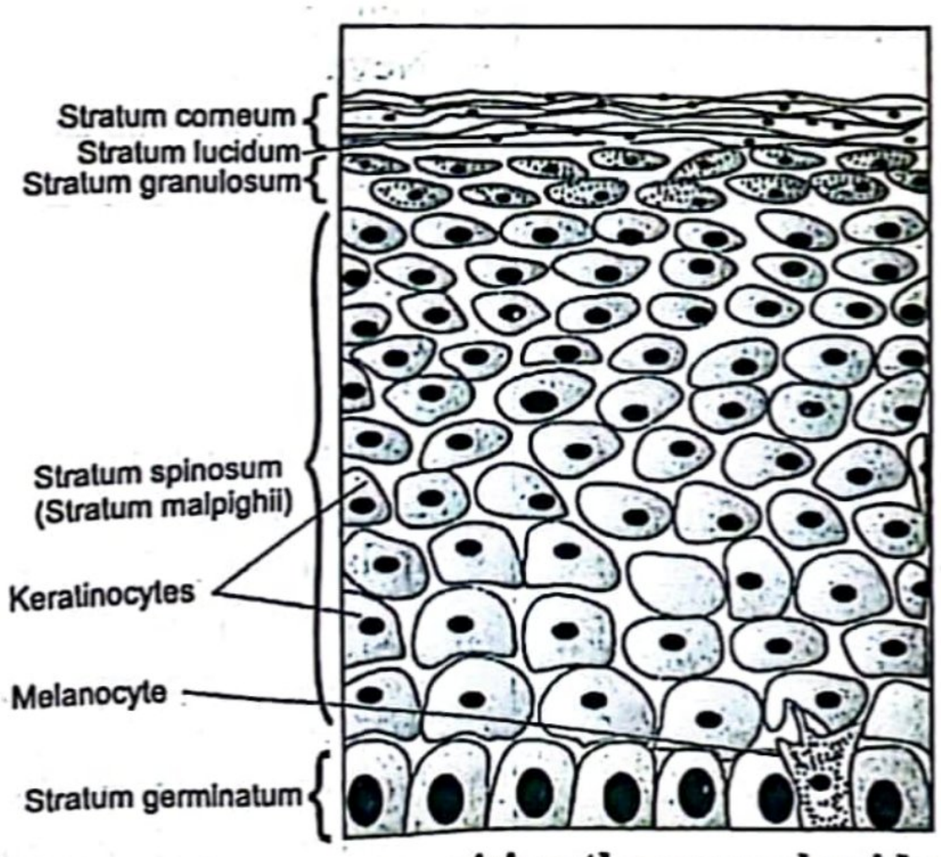


Fig: Different layers comprising the normal epidermis.

DERMIS: The dermis consists of 2 parts-

1. Superficial - papillary dermis
2. Deeper - reticular dermis.

The dermis contains ***cutaneous appendages*** or ***adnexal structures***, e.g. sweat glands, sebaceous glands, hair follicles, arrectores pilorum and nails etc.

(Ref: Robbins/10th/1133; Harsh Mohan/7th/759; Pathoma Leccture Notes)

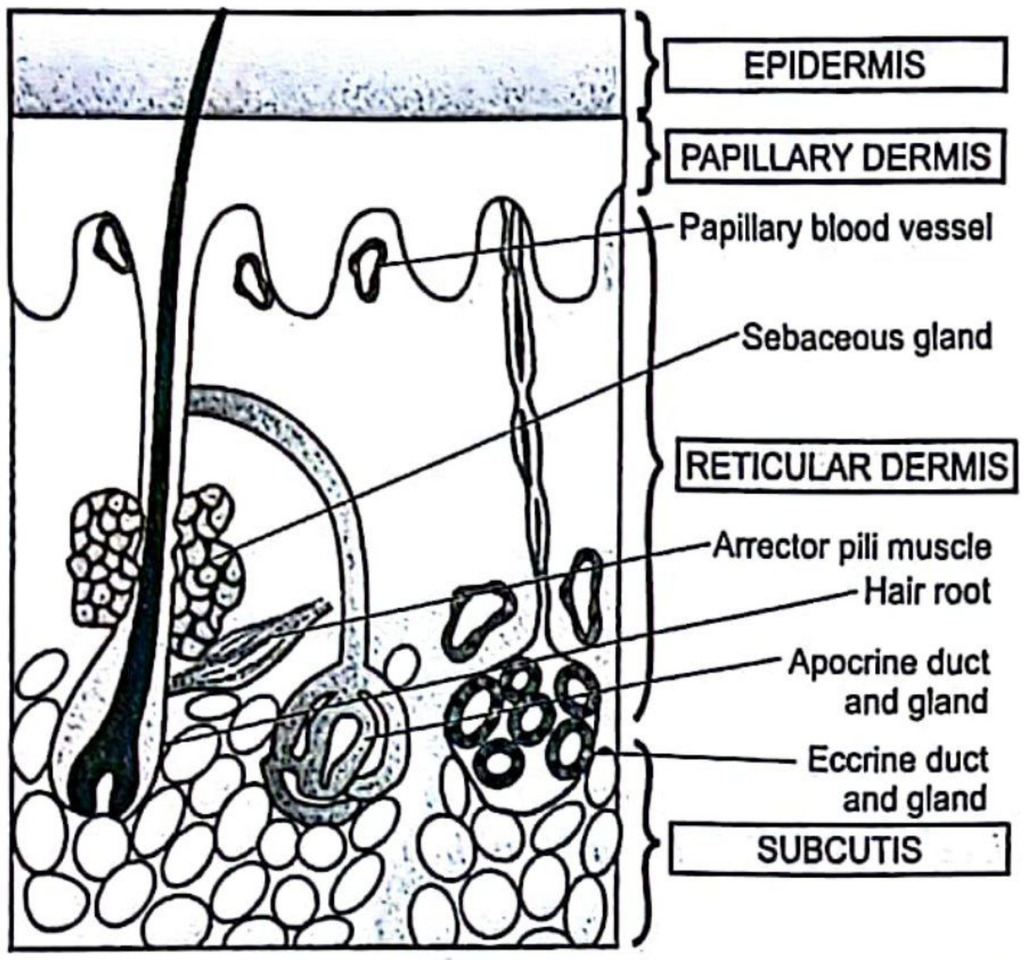


Fig: Main structures identified in a section of the normal skin.

Diseases of the Skin

Q. Mention the diseases of the skin. ***(Important for VIVA)***

Ans.

Diseases of the skin:

1. Disorders of pigmentation and melanocytes	▪ Vitiligo ▪ Albinism ▪ Freckle (Ephelis) ▪ Mesalma ▪ Lentigo ▪ Nevus (Benign neoplasm of melanocytes) ▪ Melanoma (Malignant neoplasm of melanocytes)
2. Disorders of epidermal maturation	▪ Ichthyosis
3. Acute inflammatory dermatoses	▪ Urticaria ▪ Acute eczematous dermatitis ▪ Erythema multiforme
4. Chronic inflammatory dermatoses	▪ Psoriasis ▪ Seborrhic dermatitis ▪ Lichen planus
5. Blistering (bullous) disease	▪ Inflammatory blistering disorders 1. Pemphigus 2. Bullous pemphigoid 3. Dermatitis herpetiformis ▪ Noninflammatory blistering disorders 1. Epidermolysis bullosa

Q. Classify skin tumor. (RU-17M,11/09Ju)
Q. Write the name of surface epidermal tumour. (SU-18M)
Q. What are the malignant tumours of skin? (RMU-22/21Nv,20M)
Q. Name 3 malignant neoplasms of skin. (CU-19Nv)
Q. Classify 5 common tumour of the skin. (CU-20Nv)
Q. Name the premalignant conditions of the skin. (RMU-23/22/21M, CU-20M)
Q. Name some primary skin lesion.
Ans.

Tumors of the skin: ***(Important for VIVA)***

EPIDERMAL TUMOURS	
Benign tumour	▪ Squamous papilloma ▪ Seborrhoeic keratosis ▪ Acanthosis nigricans ▪ Keratoacanthoma ▪ Fibroepithelial polyps ▪ Epithelial cyst (Wen) ▪ Benign nevus
Pre-malignant lesions	▪ Solar keratosis (actinic keratosis, senile keratosis) ▪ Bowen's disease ▪ Xeroderma pigmentosum ▪ Erythroplasia of Queyrat ▪ Leukoplakia ▪ Radiodermatitis ▪ Dysplastic nevi
Malignant tumours	▪ **Squamous cell carcinoma** ▪ **Basal cell carcinoma (Rodent ulcer)** ▪ **Malignant melanoma** ▪ **Merkel cell carcinoma**
ADNEXAL (APPENDAGEAL) TUMOURS	
▪ Tumours of hair follicles ▪ Tumours of sebaceous glands ▪ Tumours of sweat glands (e.g. sweat gland carcinoma)	
DERMAL TUMOURS	
▪ Benign fibrous histiocytoma (Dermatofibroma) ▪ Malignant fibrous histiocytoma ▪ Dermatofibrosarcoma protuberans ▪ Lipoma and liposarcoma ▪ Leiomyoma and leiomyosarcoma ▪ Haemangiomas, lymphangiomas and angiosarcoma ▪ Kaposi's sarcoma	
CELLULAR MIGRANT TUMOURS (Metastatic deposits of skin)	
▪ Mycosis fungoides (Cutaneous T-Cell Lymphoma) ▪ Langerhans' cell histiocytosis ▪ Mastocytosis ▪ Lymphomas and leukaemias ▪ Plasmacytoma	

{***N.B:*** You may tell nevus (benign neoplasm of melanocytes) & Melanoma / Malignant melanoma (malignant neoplasm of melanocytes) under separate headings MELANOCYTIC TUMOURS}.

(Ref: Robbins/10th/1142,1145; Harsh Mohan/7th/771; BRS Pathology/5th/346)

Q. What are the locally malignant tumors of skin?

Ans.

Locally malignant tumors of skin:

- Basal cell carcinoma (epidermis)
- Dermatofibrosarcoma protuberans (dermis).

(Ref: Robbins/10th/1147,1150; Harsh Mohan/7th/771; BRS Pathology/5th/346)

Q. Give the etiology & pathogenesis of basal cell carcinoma.

Q. Give the morphology of basal cell carcinoma / rodent ulcer. (RMU-21M, SU-18M)

Q. Write briefly about basal cell carcinoma. (CU-18Nv)

Q. Short note: Basal cell carcinoma. (DU-10/08Ju, CMU-23M,20Ju,19Nv,16/15Ja,13Ju, 12Ja,11/10Ju,05Ja, RMU-23M,19/18Nv,12/10/07Ja, BUP-21Nv/M, SU-13Ja)

Q. Short note: Rodent ulcer. (RU-17Nv/Ja)

Ans.

Basal cell carcinoma (Rodent ulcer): Malignant proliferation of basal cell (stem cell) of epidermis.

It is the **most common of all malignant skin tumors** arising from **basal layer of the epidermis** & its appendages. Typically, the basal cell carcinoma is a **locally invasive, slow-growing** tumour of **middle-aged** that **rarely metastasises.**

Sites: ***(Important for VIVA)***

- Chronic sun-exposed sites in **lightly pigmented** elderly adults.
- Most commonly on the **face (90%),** usually above a line from the **angle of mouth upto the ear lobule.**

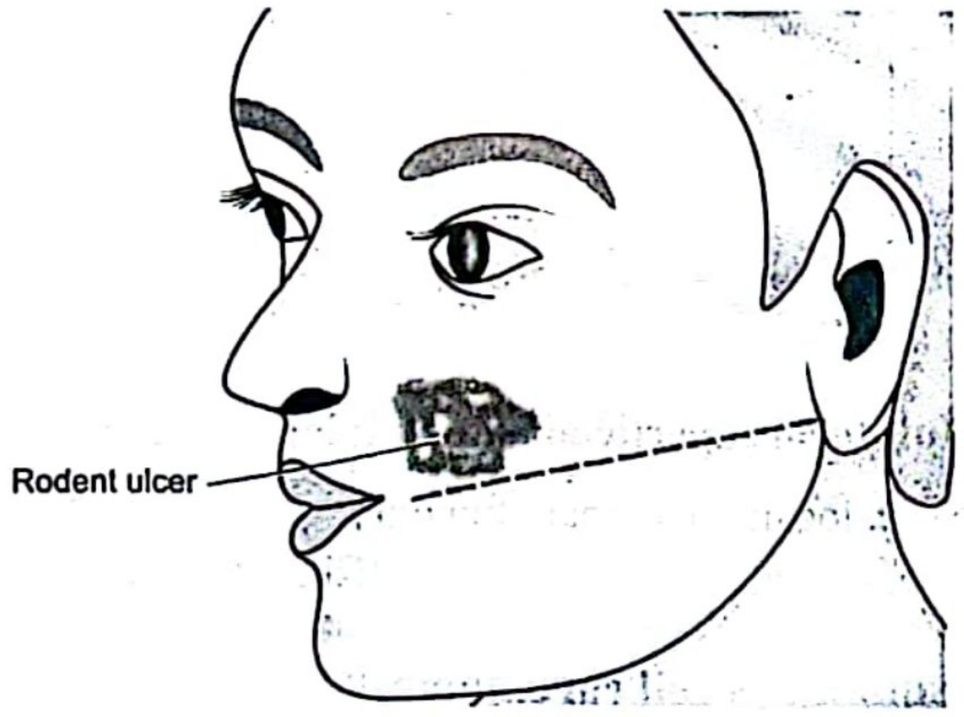


Fig: Common location and macroscopic appearance of basal cell carcinoma (rodent ulcer).

Aetiology:

i) **Age:** Mostly occur after the age of 40 years.
ii) **Race:** Lightly skinned races (who have little melanin) are most susceptible than black.
iii) **Precancerous conditions:** Xeroderma pigmentosum, basal cell nevus syndrome.
iv) **Environmental factor:** Chronic sun exposure.

Morphology:

Macroscopic:

1. **Ulcerated** (most common pattern):
   - A **slow-growing small nodule** undergoes **central ulceration** with **pearly, raised rolled margins.**
   - The tumour enlarges in size by burrowing and by destroying the tissues locally like a rodent and hence the name **'rodent ulcer'.**

2. **Non-ulcerated** (less frequent pattern): Pearly and shiny papules often containing dialated (telangiectatic) vessel.

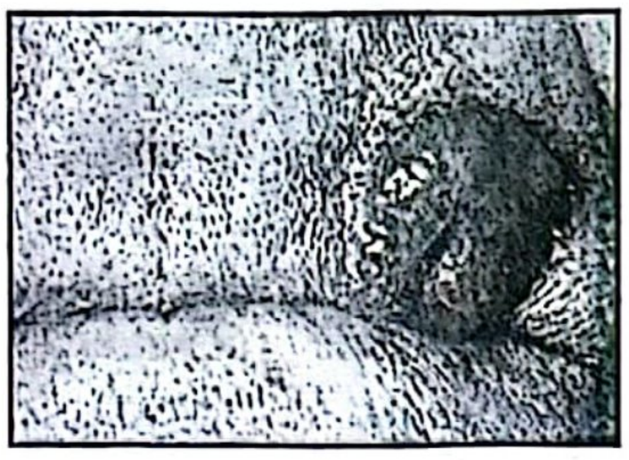


Fig: Basal cell carcinoma appears as a pearly papule with central ulceration.

Microscopic: Tumour cells resemble those in the normal basal cell layer of the epidermis. They may occur in two patterns-

- **Multifocal growth:** Extending over skin surface several square centimeters or more (multifocal superficial type).
- **Nodular lesions:** Growing downwards deeply into the dermis.

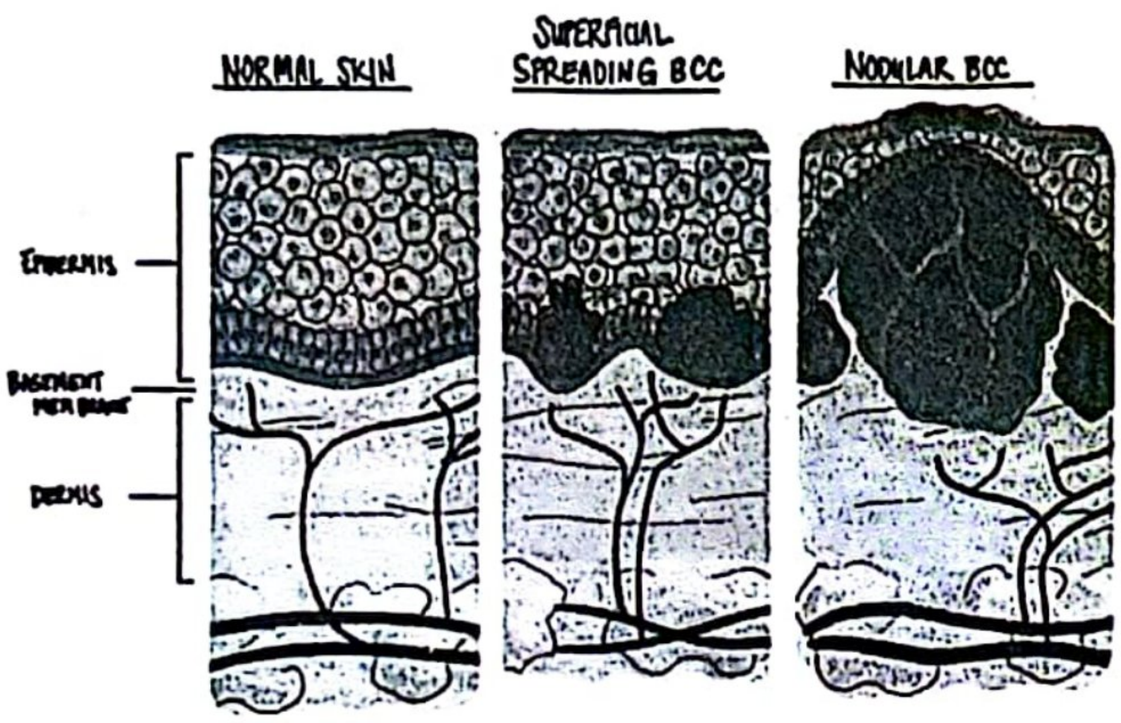


Fig: Multifocal superficial and nodular type basal cell carcinoma.

Metastasis: Rarely metastasize (i.e. locally malignant tumour).

(Ref: Robbins/10th/1147; Harsh Mohan/7th/775)

Q. Give the morphology of squamous cell carcinoma.
Q. Short note: Squamous cell carcinoma.

Ans.

Squamous cell carcinoma (Marjolin ulcer): Squamous cell carcinoma is the ***second most common*** skin cancer arising on ***sun exposed sites*** in older people.

Incidence: Higher incidence in men than in women.

Pathogenesis: The most important cause of cutaneous squamous cell carcinoma is ***DNA damage induced by exposure to UV light***. Tumor incidence is proportional to the degree of lifetime sun exposure.

Predisposing factors:

1. Prolonged sun exposure
2. Immunosupressive therapy
3. Industrial carcinogens (tars and oils)
4. Chronic ulcers and draining osteomyelitis
5. Old burn scars (Marjolin's ulcers)
6. Arsenic exposure

	2. Porphyria
6. Disorders of epidermal appendages	▪ Acne vulgaris ▪ Rosacea
7. Infection	▪ Verrucae (warts) ▪ Molluscum contagiosum ▪ Impetigo ▪ Superficial fungal infections
8. Tumors & tumour-like lesions	▪ Please see below

(Ref: Robbins/10th/1133-1169; Pathoma Lectuuree Notes)

Q. What are the inflammatory conditions of the dermis?

Ans.

Inflammatory conditions of the dermis:

1. **Acute inflammatory dermatoses:**
   - Urticaria (hives)
   - Acute eczematous dermatitis
   - Erythema multiforme
2. **Chronic inflammatory dermatoses:**
   - Psoriasis
   - Seborrhic dermatitis
   - Lichen planus.

(Ref: Robbins/10th/1153-1159)

Q. What are the blistering (bullous) diseases of skin?

Q. Classify blistering diseases of skin. (CU-19M)

Ans.

Blistering (bullous) diseases of the skin:

1. **Inflammatory blistering disorders**
   - Pemphigus
   - Bullous pemphigoid
   - Dermatitis herpetiformis
2. **Non-inflammatory blistering disorders**
   - Epidermolysis bullosa
   - Porphyria.

(Ref: Robbins/10th/1159-1164)

Tumors & Tumour-like Lesions

The skin is the largest organ of the body. Tumours and tumour like lesions may arise from different components of the skin such as:

- Surface epidermis
- Epidermal appendages &
- Dermal tissues.

Each of these tissues may give rise to:

- Benign tumours & tumour-like lesions
- Pre-malignant lesions
- Malignant tumours.

Another group of tumours have their origin from elsewhere in the body but are cellular migrants to the skin (*metastatic deposits/secondaries in skin*).

7. Psoriasis
8. HIV infection
9. Ionizing radiation
10. (In the oral cavity) tobacco and betel nut chewing
11. Precancerous condition- xeroderma pigmentosum, actinic keratosis
12. Human papilommavirus [HPV].

Sites: Squamous cell carcinoma may arise on any part of the **skin** and **mucous membranes** lined by ***squamous epithelium***. Most common locations are the **face, pinna of the ears, back of hands** and mucocutaneous junctions such as on the **lips, anal canal** and **glans penis.**

Morphology:

***Macroscopic*:** Squamous cell carcinoma of the skin and squamous-lined mucosa can have one of the following two patterns:

- More commonly, an **ulcerated growth** with elevated and indurated margin.
- Less often, a raised **fungating or polypoid growth** without ulceration.

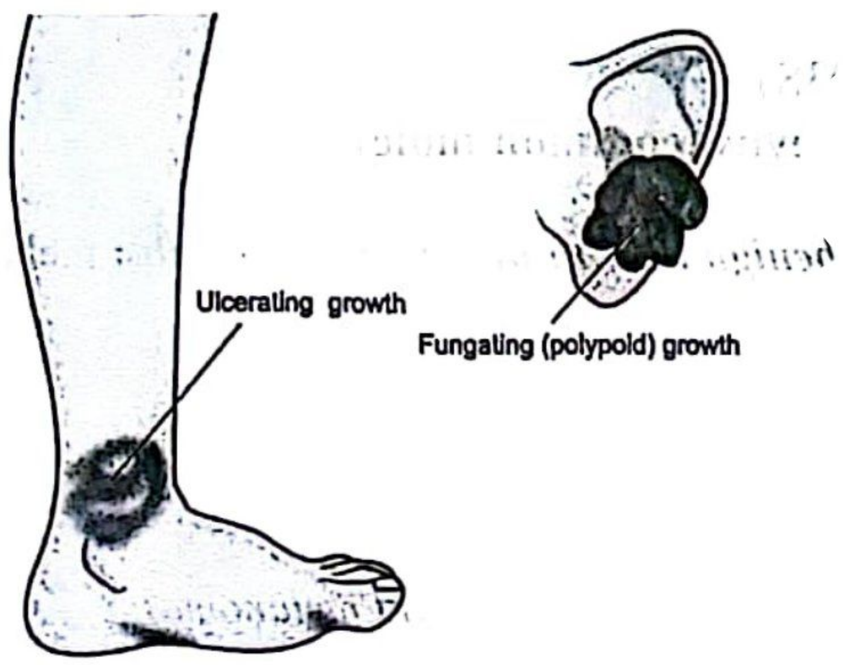


Fig: Main macroscopic patterns of squamous cell carcinoma showing ulcerated and fungating polypoid growth.

Microscopic:

- **Squamous cell carcinoma in situ** is characterized by cells with atypical (enlarged and hyperchromatic) nuclei involving all levels of the epidermis.
- **Invasive squamous cell carcinoma** shows variable degrees of differentiation, ranging from tumors composed of polygonal cells arranged in orderly lobules and having numerous large areas of keratinization, to neoplasms consisting of highly anaplastic cells that exhibit only abortive, single-cell keratinization (dyskeratosis).

(Ref: Robbins/10th/1146; Harsh Mohan/7th/774)

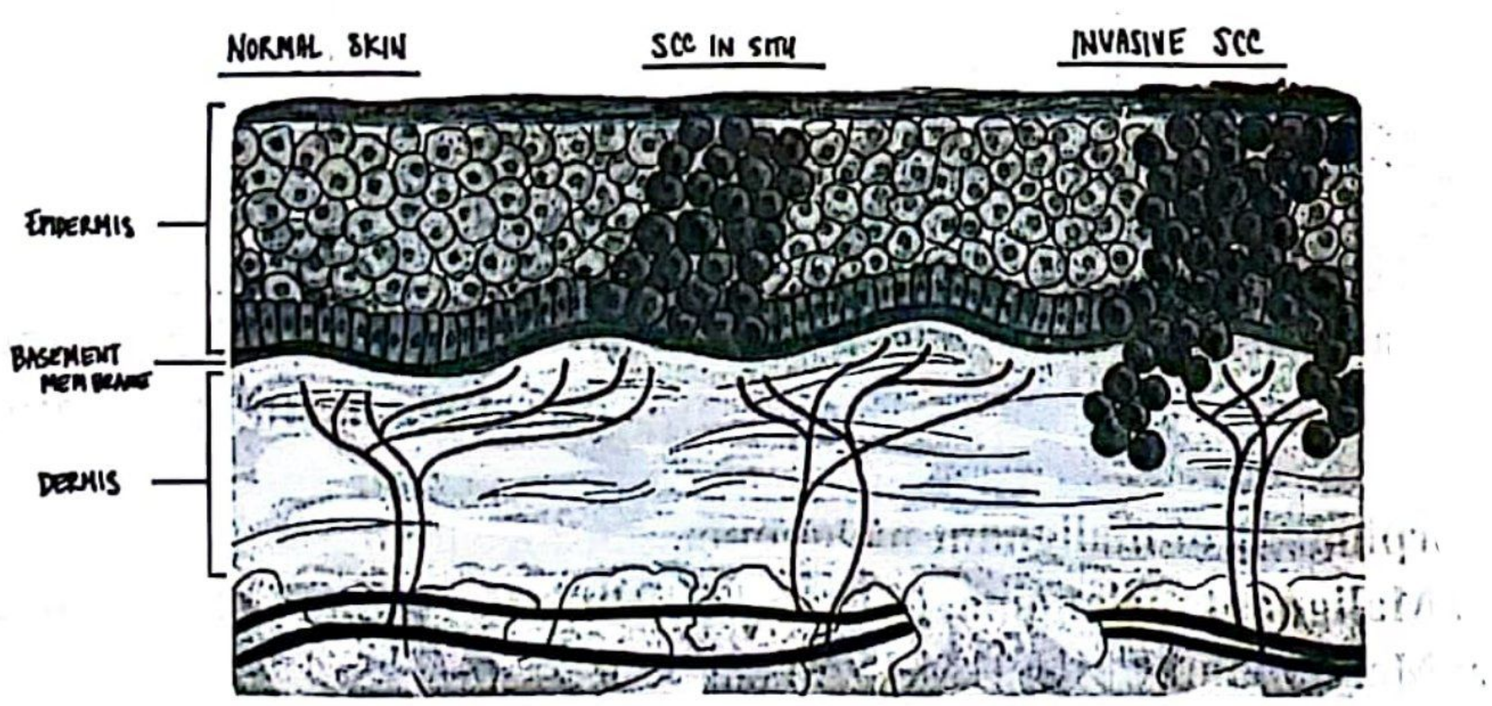


Fig: Squamous cell carcinoma in situ and invasive squamous cell carcinoma.

Investigations:

1. Skin biopsy (shave biopsy, punch biopsy, or excisional biopsy)
2. USG/CT scan to identify nodal disease
3. FNAC from the lymph node
4. MRI to identify local extension.

(N.B: Squamouus cell carcinoma may arise in skin, oral cavity, oesophagus, lungs, urinary bladder, salivary gland, and cervix etc.)

Q. A male of 72 years has developed ulcerative lesion in his right great toe for last 6 months. It is gradually spreading for last one month. He also noticed a swelling in his right inguinal region. What are the probable diagnoses? How will you investigate the patient? (BUP-16Ju)

Ans.

Probable diagnosis: Squamous cell carcinoma.

Investigation: *Please write from above.*

Q. Short note: Nevus. (DU-03S)

Q. Short note: Melanocytic nevus (common mole).

Ans.

Nevus: The term nevus denotes ***benign tumour of melanocytes***. Most melanocytic nevi are acquired.

Types of nevus:

1. Congenital nevus
2. Blue nevus
3. Spindle and epithelioid cell nevus
4. Halo nevus
5. Dysplastic nevus *(may transform into malignant melanoma)*.

Morphology:

***Gross*:**

- The lesion is tan to brown, uniformly pigmented, small (usually <6 mm across), solid regions of relatively flat (macules) to elevated skin (papules) with well-defined, rounded borders.

***Microscopic*:**

- The nevus cells may be epithelioid, cuboidal, fusiform or dendritic.
- Nuclei of nevus cells are uniform and rounded in contour, contain inconspicuous nucleoli, and show little or no mitotic activity.

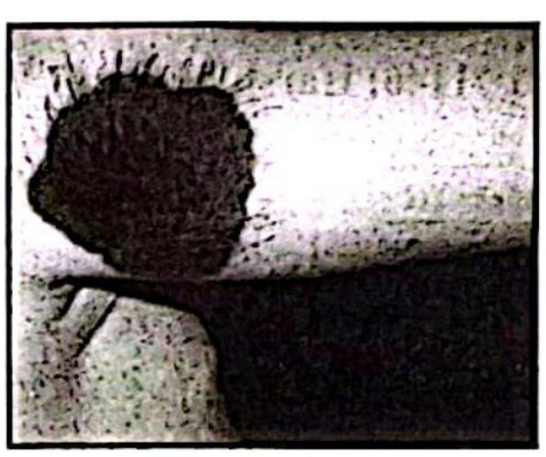


Fig: Congenital nevus.

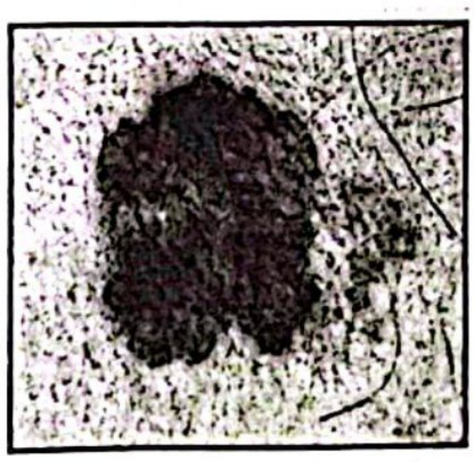


Fig: Dysplastic nevus.

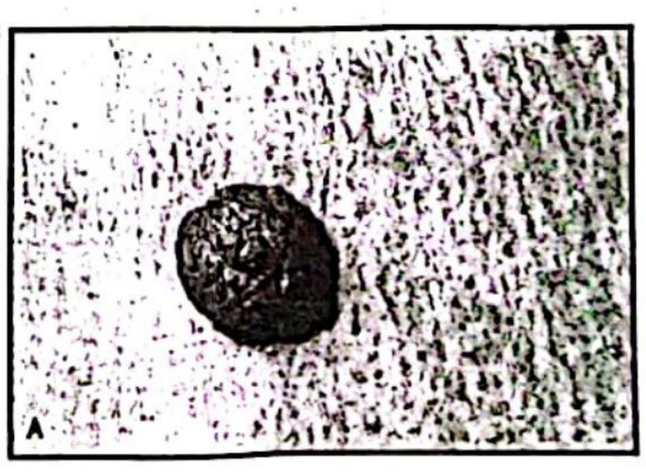


Fig: Melanocytic nevus.

(Ref: Robbins/10th/1136; BRS Pathology/5th/344)

Q. Give the morphology of malignant melanoma.

Q. Short note: Malignant melanoma. (CU-16/14/12Ju) ***(Very Important for VIVA)***

Q. Short note: Melanoma. (CMU-21M,15Ju)

Ans.

Malignant melanoma: Malignant melanoma is the **most deadly of all skin cancers** arising from melanocytes or nevus cells.

Incidence: It is most common in ***fair-skinned*** **persons** that can occur at all ages.

Predisposing factors:

1. Excessive exposure of white skin to sunlight
2. Persistent change in appearance of a mole
3. Presence of pre-existing naevus (especially dysplastic naevus)
4. Family history of melanoma in a patient of atypical mole
5. Higher age of the patient
6. Exposure to certain carcinogens.

Sites:

- Skin (*men*- upper back, *women*- back and the leg); other locations are face, soles, palms and nail-beds.
- Oral and anogenital mucosa (i.e. oropharynx, gastrointestinal and genitourinary tracts)
- Esophagus
- Conjunctiva
- Orbit
- Meninges.

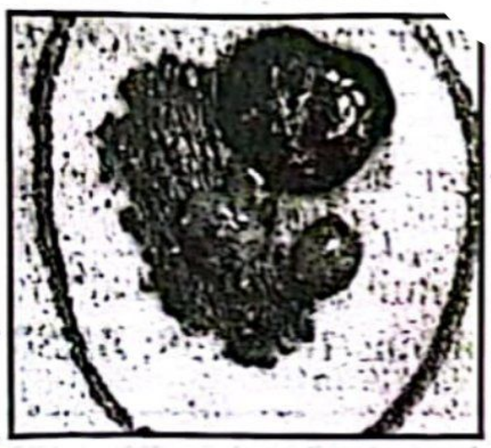


Fig: Malignant melanoma.

Clinical features:

1. Usually asymptomatic
2. Itching or pain may be early manifestations
3. Majority of the lesions are grater than 10 mm in diameter
4. Change in colour, size, or shape in a pigmented lesion are the most consistent clinical signs.

Clinical warning signs:

1. The most important **warning signs**, sometimes called the ***ABCDEs*** of melanoma, are-
   - Asymmetry
   - Irregular borders
   - Change in color
   - Increasing diameter
   - Evolution or change over time, especially if rapid.
2. Other features-
   - Pigmented lesions > 6 mm in diameter
   - Any change in appearance
   - New onset of itching or pain.

Growth pattern:

- **Radial growth (initial phase):** Growth occurs in all directions but is predominantly lateral within the epidermis and papillary zone of the dermis. During this stage of growth, melanomas do not metastasize; clinical cure is frequent.
- **Vertical growth (later phase):** Growth extends into the reticular dermis or beyond. Prognosis varies with the depth of the lesion. During this phase, lymphatics or hematogenous metastasis may occur.

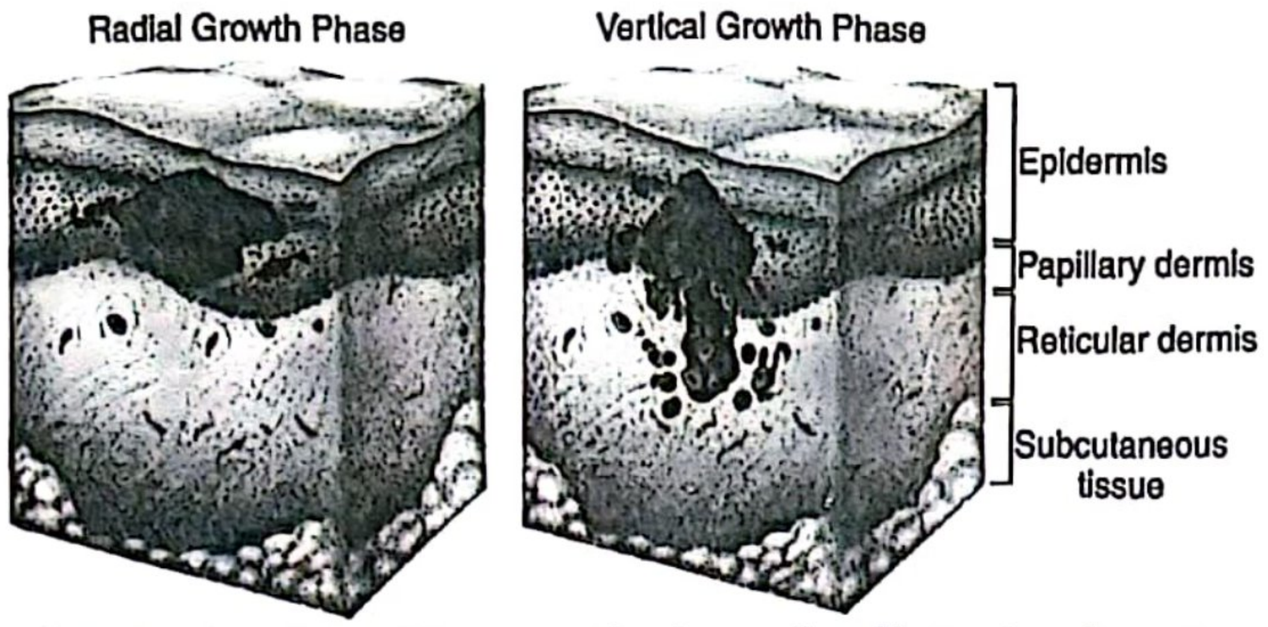


Fig: Radial and vertical growth phase of malignant melanoma.

Morphology:

Macroscopic:

- Melanomas show striking ***variations in color***, appearing in shades of black, brown, red, dark blue, and gray.
- On occasion, zones of white or flesh-colored hypopigmentation also appear.
- The ***borders*** of melanomas are ***irregular*** and often ***notched***.

Microscopic:

- Individual melanoma ***cells are larger*** than normal having large nuclei with irregular contours and prominent red (eosinophilic) nucleoli.
- The appearance of the tumor cells is similar in the radial and vertical phases of growth.

(Ref: Robbins/10th/1139; BRS Pathology/5th/347; Harsh Mohan/7th/778)

Q. A male of 70 years developed a black ulcerated lesion in his right great toe for last 6 months. It is rapidly spreading for last 2 months. Give the differential diagnosis. How will you confirm the disease? (DU-17Ja)

Ans.

Differential diagnosis:

- Malignant melanoma
- Squamous cell carcinoma

Confirmatory diagnosis: Biopsy and histopathology.

Q. A man of 70 years developed a blackih pigmented and ulcerated lesion on the sole of right foot for last 3 months. Recently right inguinal swelling is noted. What is the probable diagnosis? What is the explanation of inguinal swelling? (DU-16Ja)

Ans.

Probable diagnosis: Malignant melanoma.

Explanation of inguinal swelling: Lymphatic metastasis (vertical growth phase).

Nice to Know

DEFINITIONS OF MACROSCOPIC TERMS

Excoriation	Traumatic lesion breaking the epidermis and causing a raw linear area (i.e., deep scratch); often self-induced

Lichenification	Thickened and rough skin characterized by prominent skin markings (as lichen on a tree trunk); usually the result of repeated rubbing
Onycholysis	Separation of nail plate from nail bed
Macule	Circumscribed lesion, 5 mm or smaller in diameter, characterized by flatness and distinguished by coloration (**patch** is greater than 5 mm)
Papule	Elevated dome-shaped or flat-topped lesion 5 mm or less across (**nodule** is greater than 5 mm)
Plaque	Elevated flat-topped lesion, usually greater than 5 mm across (may be caused by coalescent papules)
Pustule	Discrete, pus-filled, raised lesion
Scale	Dry, horny, platelike excrescence; usually the result of imperfect cornification
Vesicle	Fluid-filled raised lesion 5 mm or less across (**Bulla** is greater than 5 mm. **Blister** is the common term for either.)
Wheal	Itchy, transient, elevated lesion with variable blanching and erythema formed as the result of dermal edema

(Ref: Robbins/10th/1135)

DEFINITIONS OF MICROSCOPIC TERMS

Acantholysis	Loss of intercellular cohesion between keratinocytes
Acanthosis	Diffuse epidermal hyperplasia
Dyskeratosis	Abnormal, premature keratinization within cells below the stratum granulosum
Erosion	Discontinuity of the skin showing incomplete loss of the epidermis
Exocytosis	Infiltration of the epidermis by inflammatory cells
Hydropic swelling (ballooning)	Intracellular edema of keratinocytes, often seen in viral infections
Hypergranulosis	Hyperplasia of the stratum granulosum, often due to intense rubbing
Hyperkeratosis	Thickening of the stratum corneum, often associated with a qualitative abnormality of the kfderatin
Lentiginous	A linear pattern of melanocyte proliferation within the epidermal basal cell layer.
Papillomatosis	Surface elevation caused by hyperplasia and enlargement of contiguous dermal papillae
Parakeratosis	Keratinization with retained nuclei in the stratum corneum. On mucous membranes, parakeratosis is normal.
Spongiosis	Intercellular edema of the epidermis
Ulceration	Discontinuity of the skin showing complete loss of the epidermis revealing dermis or subcutis
Vacuolization	Formation of vacuoles within or adjacent to cells; often refers to basal cell–basement membrane zone area

(Ref: Robbins/10th/1135)

CHAPTER 15

BONES, JOINTS, AND SOFT TISSUES

Osteomyelitis

Q. Define (DU-21Ja,20Nv/M,19/18M,10Ju, RU-20Nv, CU-19Nv,16/08Ja) **and classify osteomyelitis.** (DU-21Ja,20Nv/M, RU-21/19Nv)

Ans.

Osteomyelitis: Osteomyelitis denotes **inflammation of bone and marrow,** virtually always secondary to **infection.**

Osteomyelitis frequently manifests as a **primary solitary focus of disease,** but can also be a complication of any **systemic infection.** All types of organisms, including **viruses, parasites, fungi,** and **bacteria,** can produce osteomyelitis, but certain **pyogenic bacteria** and **mycobacteria** are the ***most common*** culprits.

Classification:

A) According to clinical course:

1. Acute suppurative osteomyelitis
2. Chronic osteomyelitis:
   a) Chronic suppurative osteomyelitis
   b) Tubercular osteomyelitis
   c) Syphilitic lesions of bone.

B) According to aetiology:

1. Bacterial osteomyelitis: (most common)
   - Pyogenic osteomyelitis
   - Tubercular osteomyelitis
   - Syphilitic osteomyelitis
2. Viral osteomyelitis
3. Fungal osteomyelitis
4. Parasitic osteomyelitis.

(Ref: Robbins/10th/1185)

Q. Enlist the routes of bacteria to enter into the bone.

Ans.

Routes of bacteria to enter into the bone: Bacteria my reach the bone by-

1. Haematogenous spread
2. Extension from a contiguous site
3. Direct implantation (e.g. in traumatic injury).

In adults, osteomyelitis more often occurs as a complication of ***open fractures***, ***surgical procedures***, and ***infections of the feet in the setting of diabetes***.

(Ref: Robbins/10th/1185)

Q. Give the aetiopathogenesis (CU-08Ja) **& pathology of chronic osteomyelitis.**
Q. Give the pathogenesis & complications of chronic osteomyelitis. (RU-19Nv)
Q. Mention the predisposing factors and etiologic agents of osteomyelitis. (DU-19M, CMU-23M)
Q. Describe in short the aetiopathogenesis of osteomyelitis. (DU-10Ju, CU-17M)
Q. Give the pathogenesis of suppurative osteomyelitis. (CMU-21M,11Ja)
Q. Give the pathogenesis (CU-20M) **and morphology of pyogenic osteomyelitis.** (DU-18M,15Ju)
Q. Write the morphology of pyogenic osteomyelitis. (DU-19M)
Q. Write the morphology of chronic osteomyelitis. (CMU-21M)
Q. Write the causes and pathogenesis of pyogenic osteomyelitis. (CMU-23M,16Ja)
Q. Mention the causes of osteomyelitis. (DU-18M)
Q. What are the complications of osteomyelitis? (RMU-21Nv)
Q. Write down the complications of pyogenic osteomyelitis. (RMU-22Nv)
Q. What are the complications of chronic osteomyelitis? (DU-21Ja,20Nv/M, RU-20Nv)
Q. What is involucrum? (SMU-23M)
Q. Short note: Chronic osteomyelitis. (DU-22Nv,14/13Ju,10Ja, BUP-21Nv/M) ***(V.V.I. for VIVA)***
Q. Short note: Pyogenic osteomyelitis. (DU-21Oct/M,16Ju, SU-10Ju)

Ans.

Chronic osteomyelitis: "A severe persistent and incapacitating infection of bone and bone marrow".

A) Predisposing factors:
1. History of trauma
2. Debilitation
3. Immunodeficiency state
4. Sickle cell anaemia

B) Etiologic agents:
1. **Pyogenic bacteria:**
   - *Staphylococcus aureus* (80-90%)
   - Group-B streptococci
   - *E. coli*
   - *Pseudomonas*
   - *Klebsiella*
   - *Salmonella*
   - *Haemphilus injluenzae.*
2. **Mycobacteria:** Tubercular osteomyelitis.

(Ref: Robbins/10th/1185)

Pathogenesis & morphology:

Localized infection at metaphyseal endosteum
↓
Bacteria proliferate and induce an acute inflammatory reaction and cause cell death
↓

The entrapped bone undergoes necrosis within the first 48 hours

↓

Bacteria and inflammation spread within the shaft of the bone and may percolate through the haversian system to reach the periosteum

↓

Subperiosteal abscess formation

↓

Lifting the periosteum

↓

Impair the blood supply to the affected region

↓

Ischaemia and suppurative necrosis of bone

↓

Segmental bone necrosis - formation of piece of dead bone **(Sequestrum)**

↓

Formation of soft tissue abscess

↓

Rupture of abscess through perisoteum

↓

Formation of draining sinus

After one week, chronic inflammatory cells cause fibrous growth and formation of reactive bone around the devitalized bone. Then the reactive lameller / woven bone is called **involucrum** and the interosseous sterile abscess is called **Brodie's abscess.**

(Ref: Robbins/10th/1185)

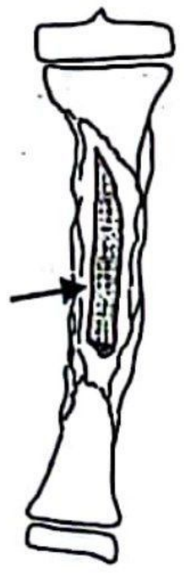


Fig: Sequestrum.

Complications of chronic osteomyelitis:

- Acute flare-up
- Pathologic fracture
- Secondary amyloidosis
- Endocarditis
- Sepsis
- Development of squamous cell carcinoma in the sinus tract
- Osteosarcoma in the infected bone (rarely).

Fig: Resected femur in a person with draining osteomyelitis.

(Ref: Robbins/10th/1186)

Q. What is sequestrum? (SMU-23M)
Q. Short note: Sequestrum. (DU-18Ja)
Ans.
Sequestrum: Sequestrum is a ***dead piece of bone*** within a living bone produced as a result of avascular necrosis results from underlying infection which is ultimately separated by osteoclast.

Cause: Chronic pyogenic osteomyelitis.

Mechanism of formation: *Please write from above.*

Fate of sequestrum: It depends on wound size:

- If small in size, can be absorbed & it will go under resolution by osteoclastic activity and absorbed by granulation tissue.
- If large in size, persists for long with chronic infection inside and discharging sinus.

(Ref: Robbins/10th/1186)

Q. What is Brodie's abscess? (SU-03Ja) ***(Very Important for VIVA)***
Ans.
Brodie's abscess: Brodie's abscess is a small intraosseous abscess that frequently involves the cortex, and is walled off by reactive bone. It is sequelae of chronic osteomyelitis.

(Ref: Robbins BASIC PATHOLOGY/10th/807)

Or,

Brodie's abscess is a circumscribed, round/oval cavity containing pus and pieces of dead bone (*sequestra*) surrounded by sclerosis.

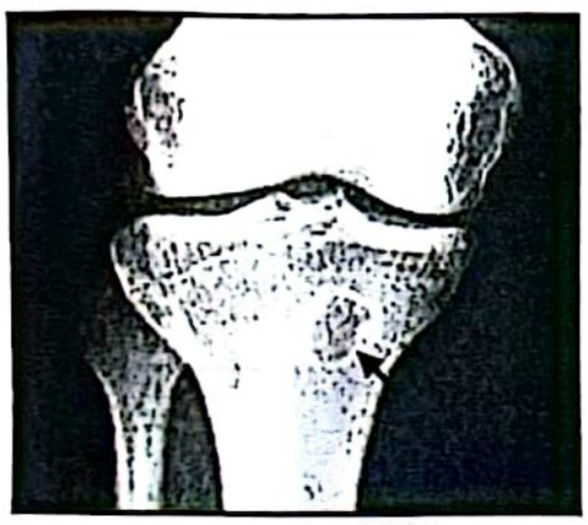


Fig: Brodie's abscess.

Q. When acute osteomyelitis turns into chronic form?
Ans.
Turning of acute osteomyelitis into chronic form: In 5-25% cases, acute osteomyelitis fails to resolve and persists as chronic infection. Chronicity may develop in following cases-

- Delay in diagnosis
- Extensive bone necrosis
- Inadequate antibiotic therapy
- Inadequate surgical debridement
- Weakened host defence.

(Ref: Robbins BASIC PATHOLOGY/10th/807)

Q. Mention the clinical features of pyogenic and tuberculous osteomyelitis.
Ans.
Clinical features of pyogenic osteomyelitis:

- Malaise
- Fever
- Chills

- Leukocytosis
- Intense throbbing pain over the infected bone
- Characteristic x-ray findings of a lytic focus of bone destruction surrounded by a zone of sclerosis.
- Blood cultures can be positive (in untreated cases).

(Ref: Robbins/10th/1186)

Clinical features of tuberculous osteomyelitis:

- Localized pain
- Low-grade fever
- Chills
- Weight loss.

(Ref: Robbins/10th/1186)

Q. What do you mean by Pott's disease?
Q. Short note: Pott's disease. (DU-19Nv)
Ans.
Pott's disease: Tuberculous osteomyelitis in the **spine** (especially the thoracic and lumber vertebra) which is the most common site of skeletal involvement of TB is known as **pott's disease.**

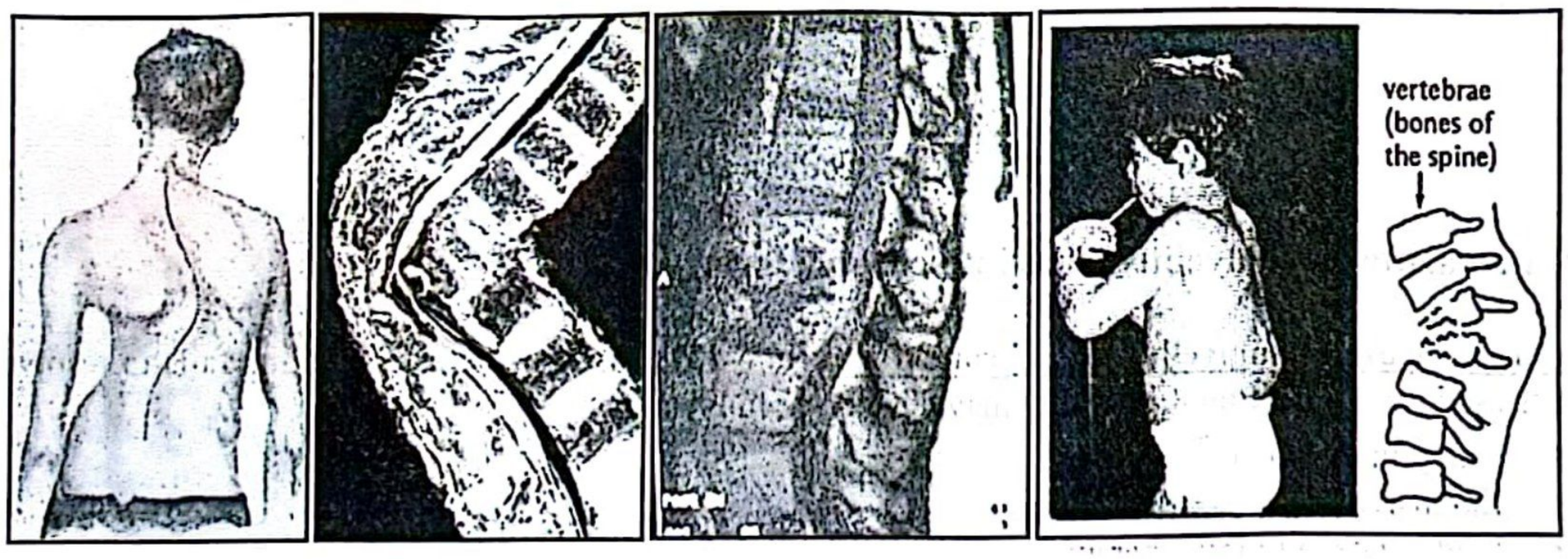
In the spine, infection breaks through intervertebral discs to involve multiple vertebrae and extends into the surrounding soft tissues, forming **abscesses.**

Clinical features:

- Localized pain
- Low-grade fever
- Chills
- Weight loss.

Complications: Discs and vertebral destruction result in **compression fractures** that culminate in **scoliosis, kyphosis,** and **neurologic deficits.**

(Ref: Robbins/10th/1186)



Q. Mention the complications of tuberculous osteomyelitis.
Ans.
Complications of tuberculous osteomyelitis:

- Permanent compression fracture of discs & vertebra produce severe scoliosis, kyphosis, and neurologic deficits
- Tuberculous arthritis
- Sinus tract formation
- Psoas abscess
- Amyloidosis.

(Ref: Robbins/10th/1186)

Q. What are the diseases associated with abnormal mineral homeostasis?
Ans.
Diseases associated with abnormal mineral homeostasis:

1. Rickets and osteomalacia
2. Hyperparathyroidism
3. Renal osteodystrophy.

Q. A young male of 16 years old complains of severe pain in the left tibia and high fever for last 7 days. His total leucocyte count is 18,000-cumm of blood. X-ray of tibia shows thickening of periosteum with focal elevation. What are your clinical diagnosis? How would you confirm this case? (DU-18Nv)
Ans.
Clinical diagnosis: Acute pyogenic osteomyelitis.

Confirmation of diagnosis (investigations):

- Blood:
  - Polymorphonuclear leucocytosis
  - Elevated ESR & CRP
  - Blood culture (at the peak of the fever) – positive in 50% of cases
- Fluid (pus) aspiration and culture
- X-rays (soft tissue swelling, perisoteal reaction, bony destruction)
- Bone scan (Tc-99)
- MRI.

Bone Tumours

Q. Classify bone tumours. (DU-09Ju, SMU-23M,14Ju,13/06Ja, CMU-21M,20Nv/Ju,19Nv,16/14/12Ju,11Ju/Ja,06S, RMU-21/19/18/17M,15/14/13/12Ju,11/10/09/08/07Ja)
Q. Classify primary bone tumours. (RMU-22M)
Q. Name five common malignant tumour of bone. (SU-10Ja,07Ju/Ja)
Q. Enumerate osteogenic bone tumours. (RMU-22/20Nv)
Q. Enumerate chondrogenic bone tumours. (RMU-23M)
Q. Name four chondrogenic bone tumours. (SU-08Ja)
Ans.

Bone tumours: ***(Very Important for VIVA)***

A) **Primary bone tumors:** Primary bone tumors are rare and are vastly outnumbered by metastases and hematopoietic tumors.

Histologic type	Benign	Malignant
Chondrogenic (40%)	Osteochondroma (most frequent) Chondroma Chondroblastoma Chondromyxoid fibroma	Chondrosarcoma (2nd most common)
Osteogenic (32%)	Osteoid osteoma Osteoblastoma	Osteosarcoma (most common)
Unknown origin (19%)	Giant cell tumor Aneurysmal bone cyst	Ewing sarcoma Adamantinoma
Notochordal (5%)		Chordoma

(Ref: Robbins/10th/1187)

B) <u>Secondary bone tumors (metastatic tumors)</u>:

1. **In adults:** From the cancers of-
   - Prostate
   - Breast
   - Kidney
   - Lung
2. **In child:** From-
   - Neuroblastoma
   - Wilms tumor
   - Osteosarcoma
   - Ewing sarcoma
   - Rhabdomyosarcoma.

(Ref: Robbins/9th/1207)

(***N.B*:** After exclusion of hematopoietic neoplasms, the **most common primary bone cancers** are **osteosarcoma, chondrosarcoma,** and **Ewing sarcoma**).

(Ref: Robbins/10th/1187)

Q. What are the bone forming tumours?

Ans.

<u>Bone forming tumours</u>: Bone forming tumors are characterized by the ***production of bone by the neoplastic cells***. The tumor bone is usually deposited as woven trabeculae (except in osteomas) and is variably mineralized. The bone forming tumors are-

Benign	Malignant
Osteoid osteoma Osteoblastoma	Osteosarcoma

(Ref: Robbins/10th/1187)

Q. What are the cartilage forming tumours?

Ans.

<u>Cartilage forming tumours</u>:

Benign	Malignant
Osteochondroma Chondroma Chondroblastoma Chondromyxoid fibroma	Chondrosarcoma

(Ref: Robbins/10th/1187,1189)

(***N.B*:** The radiographic appearance of metastases may be ***lytic*** **(bone destroying),** ***blastic*** **(bone forming),** or ***mixed*** **lytic and blastic**).

(Ref: Robbins/10th/1196)

Q. Write in brief about osteosarcoma. (SMU-23M, RMU-22/21M,18/17M,08Ja)
Q. Write down the morphology of osteosarcoma. (DU-09Ju, CMU-22Nv,10Ju,08/07Ja, SU-14Ju, RU-13/12Ju,10/07Ja)
Q. Describe the histopathological findings of osteosarcoma. (SU-07Ja)
Q. Write the microscopic features of osteosarcoma. (CU-13Ju)
Q. Describe the morphology of osteogenic sarcoma. (CU-06S)
Q. Short note: Morphology of osteosarcoma. (RU-20M)

Q. Short note: Osteosarcoma. (DU-09Ja,07Ju, SMU-23/20M,16Ja, BUP-22M, CMU-22M,14Ja,12Ju, RU-19M,17/ 16Ju)

Ans. ***(Very Important for VIVA)***

Osteosarcoma: Osteosarcoma is the **most common primary malignant tumor of bone** and accounts for approximately 20% of bone cancers.

Age group: The age distribution of osteosarcoma is **bimodal,** with 75% occurring **before 20 years of age.** A smaller peak occurs in older adults (**after 60 years of age**), in whom it is frequently associated with predisposing conditions such as **Paget disease of bone, infarcts,** and **prior radiation** (sometimes called ***secondary osteosarcomas***). Men are affected slightly more often than women (1.6 : 1).

Sites of origin: Although any bone can be involved, tumors usually arise in the **metaphyseal region** of the **long bones;** almost **50%** are near the knee in the **distal femur** or **proximal tibia.**

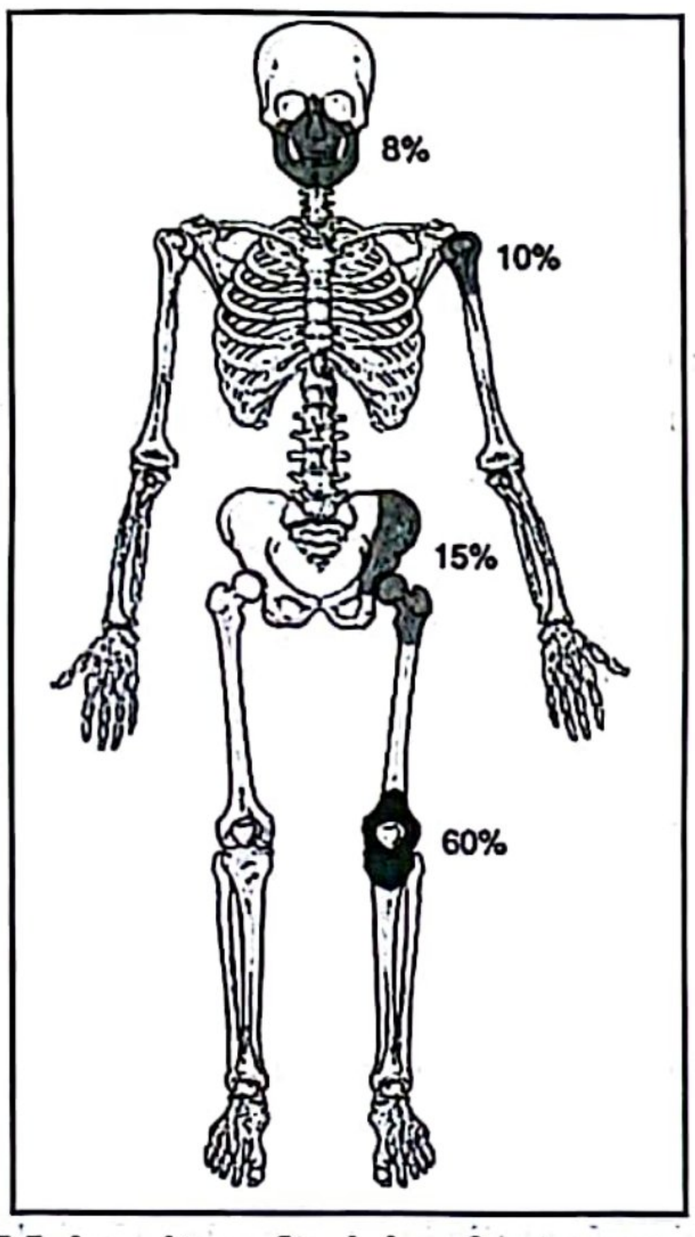


Fig: Major sites of origin of osteosarcomas.

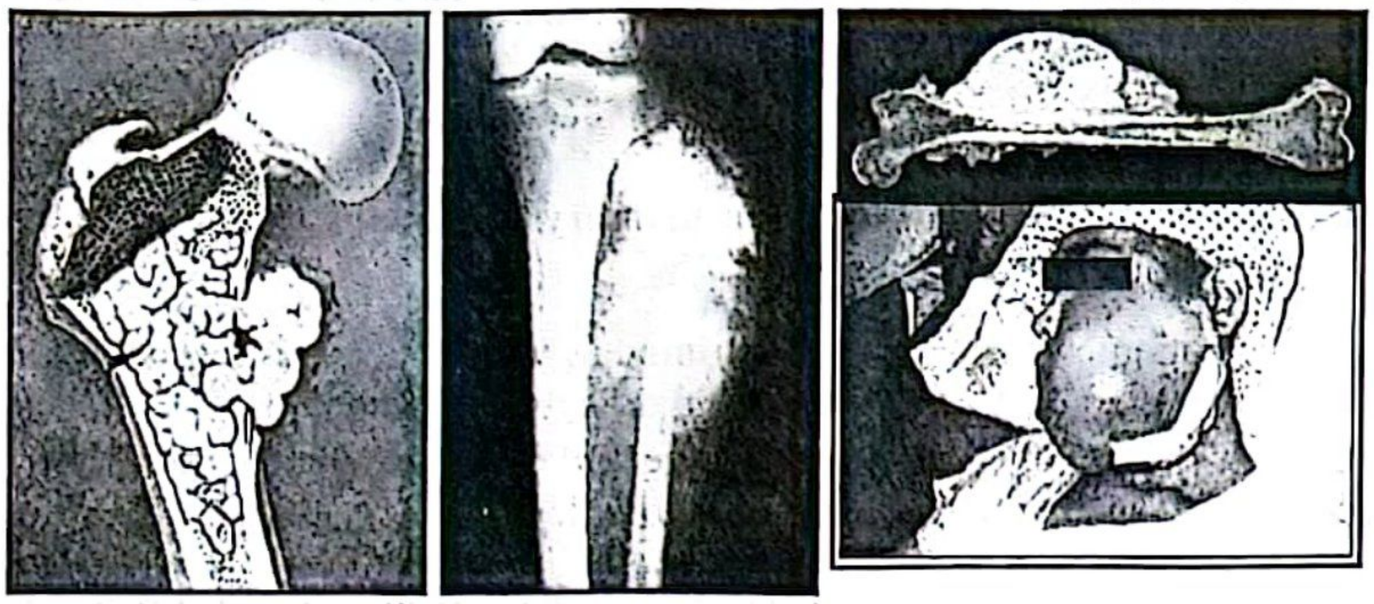
Morphology:

***Gross*:**

- Osteosarcomas are bulky, gritty, gray-white tumors that often contain hemorrhage and cystic degeneration.
- The tumours frequently destroy the surrounding cortices and produce soft tissue masses.
- The tumors spread extensively in the medullary canal, and replace hematopoietic marrow.
- Infrequently, they penetrate the epiphyseal plate, or enter the joint.

***Microscopic*:**

- The tomour cells vary in size and shape (pleomorphism) and frequently have large hyperchromatic nuclei.
- Bizarre tumor giant cells, and abundant mitoses including abnormal (e.g. tripolar) forms are common.
- Extensive necrosis and intravascular invasion are also common.
- Neoplastic cells can also produce cartilage; if abundant, such tumors are classified as *chondroblastic osteosarcoma.*



Clinical features:

1. Painful progressively enlarged mass
2. Pathologic fractures.

Metastases: To the lungs, bones, brain, and elsewhere.

(Ref: Robbins/10th/1188)

(***N.B*: Radiographically,** the enlarging tumor forms a destructive, **mixed lytic and blastic mass** with infiltrative margins. The tumor frequently breaks through the cortex and lifts the periosteum, inducing **reactive periosteal bone formation**. The triangular shadow between the cortex and raised periosteal ends, known radiographically as a ***Codman triangle,*** indicates an aggressive tumor.)

(Ref: Robbins/10th/1188)

Q. A male aged 17 years presents with pain and progressive swelling around the right knee. X-ray shows mixed osteoblastic and lytic mass at the lower part of femur. What is your diagnosis?
Ans.
Diagnosis: Osteosarcoma.

Q. Describe the histopathological findings of chondrosarcoma.
Q. Short note: Chondrosarcoma.
Ans.
Chondrosarcoma: Chondrosarcomas are **malignant cartilage-producing tumors**. After osteosarcoma, chondrosarcoma is the **second most common** malignant matrix-producing tumor of bone.

They are subclassified histologically as *conventional*, *clear cell*, *dedifferentiated*, and *mesenchymal variants*.

Age group: Individuals with chondrosarcoma are usually in their **40s or older**, and men are affected twice as frequently as women.

Sites of origin: Chondrosarcomas commonly arise in the axial skeleton, especially the pelvis, shoulder, and ribs, but, unlike benign enchondroma, distal extremities are rarely involved.

Morphology:

Gross:

- Conventional chondrosarcomas are large bulky tumors made up of nodules of glistening gray-white, translucent cartilage, but the matrix is often gelatinous or myxoid and can ooze from the cut surface.
- Spotty calcifications are typically present, and central necrosis may create cystic spaces.
- Tumor spreads through the cortex and into surrounding muscle and fat.

Microscopic:

- The malignant cartilage infiltrates the morrow space & surrounds pre-existing bony trabeculae.

- The tumors vary in degree or cellularity, cytologic atypia & mitotic activity.

(Ref: Robbins/10th/1191)

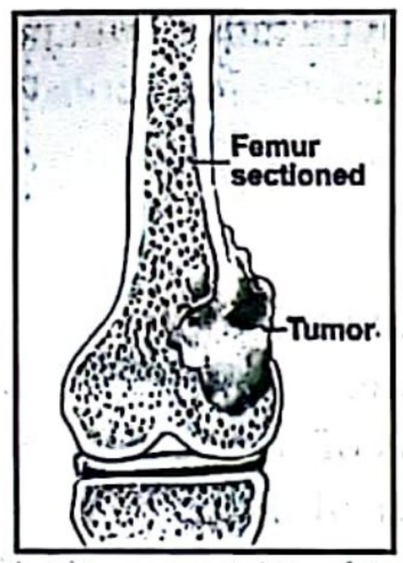


Fig: Chondrosarcoma.

Q. Write down in brief about Ewing sarcoma. (SMU-23M)
Q. Short note: Ewing sarcoma. (DU-17Ja, RU-19/17M;16Ju)
Q. Short note: Ewing tumor. (DU-05Ja)

Ans.

Ewing sarcoma: Ewing sarcoma is a **malignant bone tumor** characterized by **primitive round cells** without obvious differentiation.

It accounts for approximately 6% to 10% of primary malignant bone tumors and the **second most common group of bone sarcomas in children.**

Age group: Most affected individuals are 10 to 15 years old, and approximately 80% are younger than 20 years. Boys are affected slightly more frequently than girls.

Sites of origin: Ewing sarcoma usually arises in the **diaphysis** of long tubular bones, especially the femur and the flat bones of the pelvis and presents as a painful, enlarging mass.

Morphology:

***Gross*:**

- Ewing sarcoma usually arises in the medullary cavity and invades the cortex, periosteum, and soft tissue.
- The tumor is soft, tan-white, and frequently contains areas of hemorrhage and necrosis.

***Histology*:**

- It is composed of sheets of uniform small, round cells with scant cytoplasm that may be clear due to abundant glycogen.
- The presence of **Homer-Wright rosettes** (which are rounded cell clusters with a central fibrillary core) indicates neuroectodermal differentiation.
- Fibrous septae may also be present, but there is little stroma.
- Geographic necrosis may be prominent.

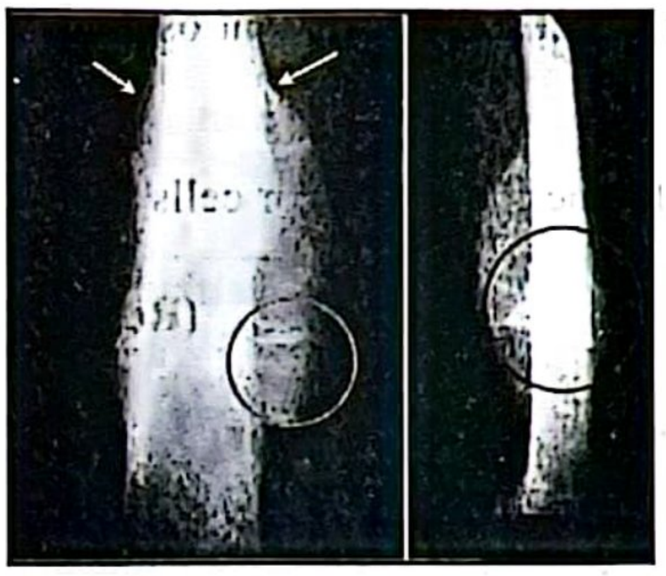


Fig: Ewing tumour in X-ray.

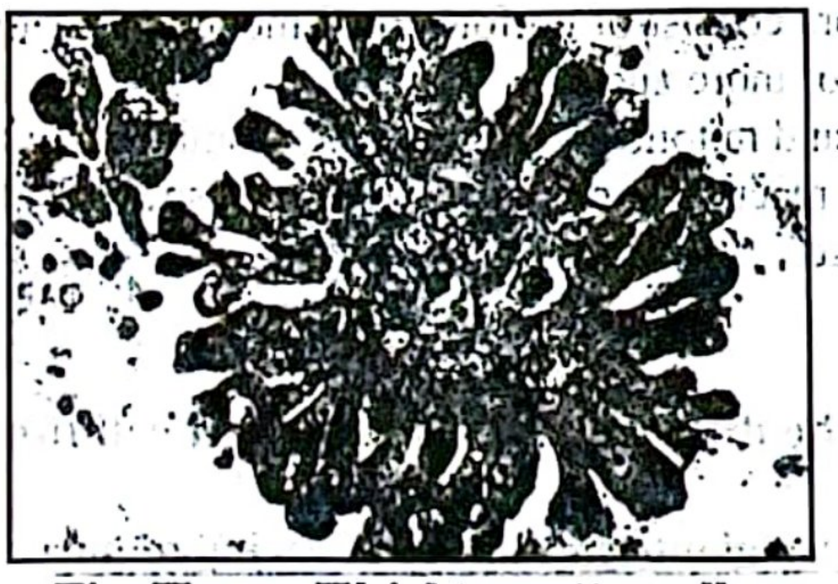


Fig: Homer-Wright rosettes cells.

Clinical features:

1. Present as painful enlarging masses and the affected site is frequently tender, warm and swollen.
2. Some may have fever, high ESR, anemia, leukocytosis.
3. Plain radiograph shows a destructive **lytic** tumor with permeative, or moth-eaten, margins that extend into surrounding soft tissues. The characteristic periosteal reaction produces layers of reactive bone deposited in an **onion-skin fashion.**

(Ref: Robbins/10th/1192)

Q. Write the morphology of giant cell tumour of bone. (SU-18M,10Ja, RU-13/12Ju, CU-12Ja)
Q. Give the morphology of giant cell tumour. Write it's behavior. (SU-08Ja,07Ju)
Q. Name the giant cell containing lesions of bone. (SU-18M,15Ju)
Q. Mention brief about giant cell tumour of bone. (SMU-23M, RMU-22/21M,18M,11Ja)
Q. Short note: Giant cell tumour of bone. (DU-08Ja, SU-20Nv,14/12Ja,11Ju,06Ja, RU-17Ja,15Ju,10Ja, CU-15/13Ja)
Ans.

Giant cell tumour: Giant cell tumor is so named because it is characterized by the presence of **numerous multinucleated osteoclast-type giant cells,** and is also called ***osteoclastoma.***

Although giant cell tumors are **benign,** they can be **locally aggressive.**

Age group: This uncommon tumor usually arises in the **third to fifth decades of life.**

Sites of origin: Giant cell tumors develop within the **epiphysis** and may extend into the metaphysis. The majority are near the knee, involving the distal femur or proximal tibia, but virtually any bone can be involved.

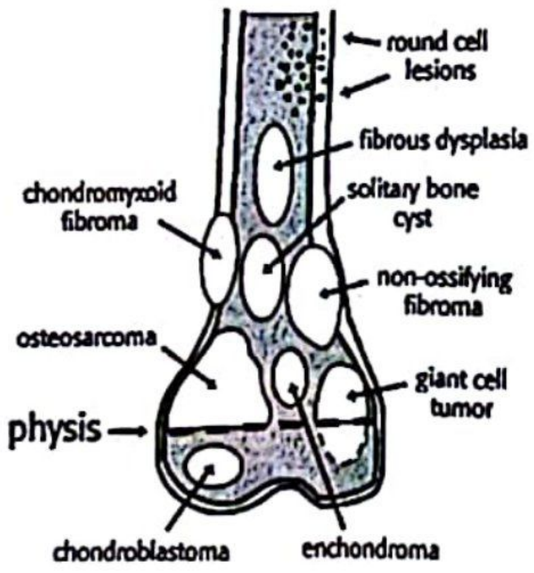


Fig: Giant cell tumour.

Morphology:

***Macroscopically*:**

- The tumors are large and red brown mass.
- They frequently undergo cystic degeneration.

***Microscopically*:**

- The tumors consist of uniform oval mononuclear tumor cells and abundant osteoclast-type giant cells with 100 or more nuclei.
- Necrosis and mitotic activity may be prominent.
- Although reactive bone may be present, especially at the periphery, tumor cells do not synthesize bone or cartilage.

(Ref: Robbins/10th/1193)

Q. Enumerate the differences between giant cell tumour & Ewing tumor.
Ans.

Differences between giant cell tumour & Ewing tumor:

Giant cell tumour	Ewing tumor
1. **Age of onset:** 20-40 years	1. **Age of onset:** children & young adults (approx. 80% are younger than 20 years)
2. Locally malignant	2. Primary malignant
3. Almost always arise in the epiphysis of long bones	3. Most often are centered in the diaphysis
4. **Morphology:** Multinucleated giant cells within the back ground of the mononuclear cells	4. **Morphology:** Small, round cells with small amount of clear cytoplasm and presence of **Homer-Wright rosettes**

(Ref: Robbins/10th/1192,1193)

Q. What do you mean by soft tissue tumour? (CU-20M) **Give three examples of soft tissue tumour?** (CU-17M)
Q. Classify soft tissue tumours. (CMU-22M)
Q. Short note: Soft tissue tumour. (CU-19M)
Ans.
Soft tissue tumor: Soft tissue tumour refers to the tumors originate in fibrous connective tissue, adipose tissue, skeletal muscle, joint tissue, and the peripheral nervous system.

(***N.B:*** In terms of clinical and pathologic entities, **soft tissue** refers to ***non-epithelial tissue*** excluding the skeleton, joints, central nervous system, hematopoietic and lymphoid tissues).

Examples of soft tissue tumor:

- Lipoma (***benign*** tumor of mature adipose tissue) - *most common soft tissue tumor*
- Liposarcoma (***malignant*** tumor of adipose tissue)
- Rhabdomyoma (***benign*** tumor of skeletal muscle)
- Rhabdomyosarcoma (***malignant*** tumor of skeletal muscle)
- Leiomyoma (***benign*** tumor of smooth muscle)
- Leiomyosarcoma (***malignant*** tumor of smooth muscle)
- Hemangioma (vascular ***benign*** tumour)
- Angiosarcoma (vascular ***malignant*** tumour)
- Schwannoma (***benign*** tumour of the peripheral nerve sheath)
- Neurofibroma (***benign*** tumour of the peripheral nerve sheath)
- Malignant peripheral nerve sheath tumor
- Synovial sarcoma (***malignant*** soft tissue tumor originates in tissue adjacent to a joint)
- Fibrous histiocytoma (***benign*** tumor consisting of a mixture of fibroblasts and histiocytes)
- Undifferentiated pleomorphic sarcoma ("***malignant*** fibrous histiocytoma")
- Fibrosarcoma (***malignant*** tumor of fibroblasts).

(Ref: Robbins/10th/1208; BRS Pathology/5th/364)

Arthritis

Q. Enumerate the causes of arthritis.
Ans.
Arthritis: Arthritis refers to inflammation of joints.

Causes of arthritis:

1. Seropositive arthritis	Rheumatoid arthritis Juvenile idiopathic arthritis (JIA)
2. Seronegative arthritis	**R**eactive arthritis (Reiter syndrome) **A**nkylosing spondylitis **P**soriatic arthritis **E**nteropathic arthritis

RAPE

3. Infectious arthritis	Suppurative arthritis (*Gonococcus, Staphylococcus, Streptococcus, H. influenzae*, gram-negative bacilli e.g. *E. coli, salmonella, pseudomonas*) Tuberculous arthritis Lyme arthritis Viral arthritis (parvovirus, rubella, and hepatitis C virus)
4. Degenerative & metabolic arthritis	Osteoarthritis Gout and gouty arthritis

(Ref: Robbins/10th/1197)

Q. Name 2 systemic diseases that affect joints. (DU-09Ja)

Ans.

Systemic diseases that affect joints:

- Rheumatic fever
- SLE.

Nice to Know:

Osteoarthritis (OA): Osteoarthritis (OA), also called ***degenerative joint disease***, is characterized by **cartilage degeneration** that results in structural and functional failure of synovial joints. It is the most common type of joint disease.

(Ref: Robbins/10th/1198)

Q. Give in short the pathogenesis (CU-19M) **& pathology of rheumatoid arthritis.**

Ans.

Rheumatoid arthritis (RA): Rheumatoid arthritis (RA) is a chronic **autoimmune disorder** that principally attacks the joints, producing a **non-suppurative proliferative** and **inflammatory synovitis.**

RA often progresses to **articular cartilage destruction** and, in some cases, **joint fusion** ***(ankylosis)***.

Extraarticular lesions may involve skin, heart, blood vessels, and lungs, leading to clinical manifestations that overlap with other autoimmune disorders including systemic lupus erythematosus and scleroderma.

(Ref: Robbins/10th/1199)

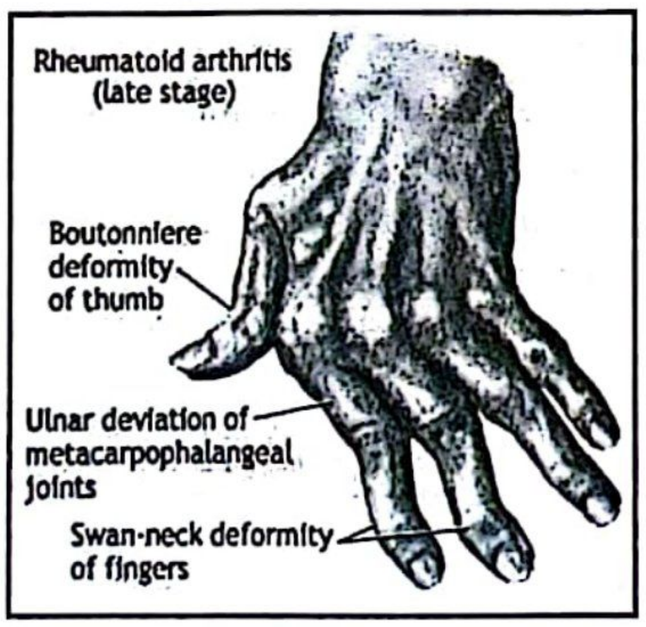


Fig: Rheumatoid arthritis (RA).

Occurrence: RA is three times more common in women than in men. It is most common in those aged 40 to 70, but no age is immune.

Pathogenesis: RA is an ***autoimmune disease***, in which the pathologic changes are mediated by ***antibodies against self-antigens*** and ***inflammation*** caused by cytokines, predominantly secreted by CD4+ T cells. **CD4+ T helper (T_H) cells initiate the autoimmune response** by reacting with an ***arthritogen***, perhaps microbial or a chemically modified self-antigen.

Continuing autoimmune reaction

↓

Activation of CD4+ T helper (T_H) cells and other lymphocytes
↓
Local release of inflammatory mediators and cytokines
↓
Destruction of bone and cartilage in joints.

Mediators (cytokines) produced by T-cells and their role in tissue (joint) injury:

- IFN-γ from T_H1 cells activates macrophages and synovial cells.
- IL-17 from T_H17 cells recruits neutrophils and monocytes.
- RANKL expressed on activated T cells stimulates osteoclasts and bone resorption.
- TNF and IL-1 from macrophages stimulate resident synovial cells to secrete proteases that destroy hyaline cartilage.

Morphology:

1. **Joints:**
   - RA typically affects small joints of the hands and feet.
   - The synovium becomes grossly edematous, thickened, and hyperplastic.
   - The characteristic histologic features include:
     - Synovial cell hyperplasia and proliferation.
     - Dense inflammatory infiltrates (frequently forming lymphoid follicles) of CD4+ helper T cells, B cells, plasma cells, dendritic cells, and macrophages.
     - Increased vascularity due to angiogenesis.
     - Fibrinopurulent exudate on the synovial and joint surfaces.
     - Osteoclastic activity in subchondral bone, allowing the inflamed synovium to penetrate the bone and cause periarticular erosions and subchondral cysts.
     - Pannus formation (exuberant synovium is known as pannus).
2. **Tendino-muscular involvement:** Focal areas of inflammation in tendons, ligaments and adjacent skeletal muscle.
3. **Skin:** Subcutaneous rheumatoid nodules appear in elbows, ulnar aspect of the forearm, occiput, and lumbosacral area.
4. **Blood vessels:** A nonspecific acute vasculitis may appear.
5. **Eye:** Nonspecific conjunctivitis or uveitis.
6. **Other organs:** Nonspecific inflammatory changes may be found in the lungs, pleura, pericardium, myocardium and peripheral nerves.

(Ref: Robbins/10th/1199; Pocket Companion to Robbins/7th/648,649)

Nice to Know:

Comparative features of osteoarthritis and rheumatoid arthritis:

	Osteoarthritis	Rheumatoid Arthritis
Primary pathogenic abnormality	Mechanical injury to articular cartilage	Autoimmunity
Role of inflammation	May be secondary; inflammatory mediators exacerbate cartilage damage	Primary: cartilage destruction is caused by T cells and antibodies reactive with joint antigens
Joints involved	Primarily weight bearing (knees, hips)	Often begins with small joints of fingers; progression leads to multiple joints involved
Pathology	Cartilage degeneration and fragmentation, bone spurs, subchondral cysts; minimal inflammation	Inflammatory pannus invading and destroying cartilage; severe chronic inflammation; joint fusion (ankylosis)
Serum antibodies	None	Various, including ACPA, rheumatoid factor
Involvement of other organs	No	Yes (lungs, heart, other organs)

(Ref: Robbins/10th/1197)

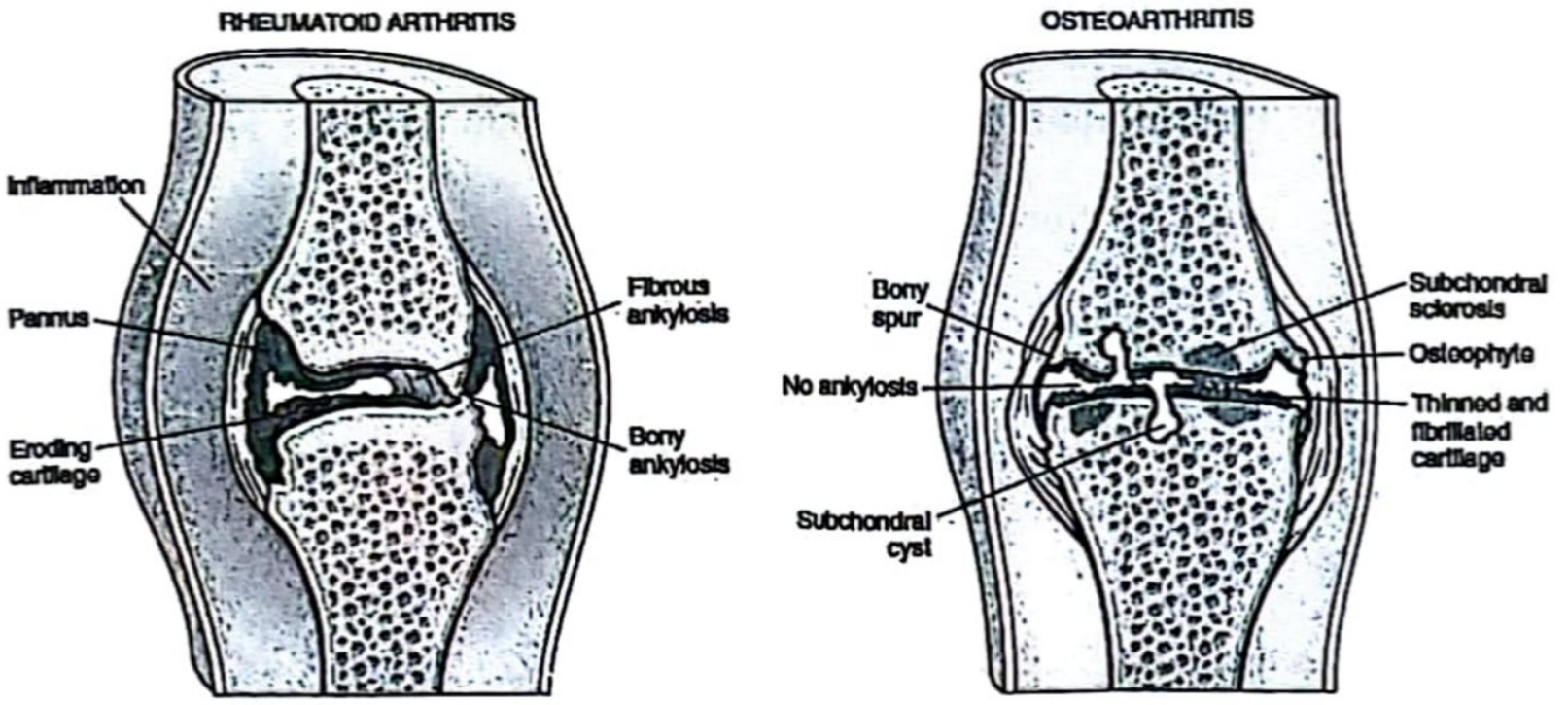


Fig: Comparison of the morphologic features of rheumatoid arthritis and osteoarthritis.
(Ref: Robbins/10th/1200)

Q. What is Reiter syndrome? (For VIVA)

Ans.

Reiter syndrome: Reiter syndrome is a form of reactive arthritis and is defined by a ***triad*** of arthritis, non-gonococcal urethritis or cervicitis, and conjunctivitis.

(Ref: Robbins/9th/1213)

Q. Short note: Pathological bone fracture. (RU-08Ju)

Ans.

Pathological bone fracture: Fracture in a diseased bone following minor injury.

Causes:

1. Inflammatory	Chronic oeteomyelitis
2. Neoplastic	**a. Benign:** Osteoclastoma **b. Malignant:** ▪ Primary- Osteosarcoma, Ewing's tumor ▪ Secondary (common) - Thyroid, kidney, breast
3. Metabolic	Osteoporosis, osteomalacia
4. Cystic	Aneurismal bone cyst

CHAPTER 16

THE CENTRAL NERVOUS SYSTEM

Q. What are the infective conditions of CNS?

Ans.

Infective conditions of CNS: *(Important for VIVA)*

- **Acute meningitis**
  - Acute pyogenic (bacterial) meningitis
  - Acute aseptic (viral) meningitis
- **Acute focal suppurative infections**
  - Brain abscess
  - Subdural empyema
  - Extradural abscess
- **Chronic bacterial meningoencephalitis**
  - Tuberculosis
  - Neurosyphilis
  - Neuroborreliosis (Lyme disease)
- **Viral meningoencephalitis**
  - Arthropod-borne viral encephalitis (Arboviruses)
  - Herpes simplex virus (Type 1 & Type 2)
  - Varicella-Zoster virus (Herpes zoster)
  - Cytomegalovirus
  - Polio virus
  - Rabies virus
  - HIV
  - Progressive multifocal leukoencephalopathy
  - Subacute sclerosing panencephalitis
- **Fungal meningoencephalitis**
  - *Candida albicans*
  - *Aspergillus fumigatus*
  - *Cryptococcus neoformans*

- **Protozoal diseases**
  - Malaria
  - Toxoplasmosis
  - Amebiasis
  - Trypanosomiasis
- **Rickettsial infections**
  - Typhus
  - Rocky Mountain spotted fever
- **Metazoal diseases**
  - Cysticercosis
  - Echinococcosis.

(Ref: Robbins/10th/1241,1261-1269)

Q. Name some viruses causes CNS infection.

Q. What are the neurotrophic viruses?

Ans.

Neurotrophic viruses:

1. Polio virus
2. Rabies virus
3. Herpes simplex virus (type 1 & type 2)
4. Varicella-Zoster virus
5. Cytomegalovirus
6. HIV
7. Mumps
8. Measles
9. Arboviruses
10. Coxsackie virus
11. Echo virus.

(Ref: Robbins/10th/1264)

Q. Define meningitis and meningoencephalitis?

Ans.

Meningitis: Meningitis is an **inflammatory process of the leptomeninges and CSF** within the subarachnoid space, usually caused by an infection.

It is usually caused by an infection, but may also occur in response to non-bacterial irritant (e.g. **chemical meningitis**). Infectious meningitis is broadly classified into **acute pyogenic** (usually bacterial meningitis) meningitis, **aseptic** (usually acute viral meningitis), and **chronic** (usually tuberculous, sphirochetal, or cryptococcal) meningitis.

Although infections are the most common causes of meningitis and meningoencephalitis, this reaction may also occur in response to a nonbacterial irritant introduced into the subarachnoid space ***(chemical meningitis)*** or in the context of a systemic autoimmune disease. Based on the etiology and clinical evolution of the illness, infectious meningitis is broadly classified into ***acute pyogenic*** (usually bacterial), ***aseptic*** (usually acute or subacute viral), and ***chronic*** (usually tuberculous, spirochetal, or cryptococcal).

Meningoencephalitis: Meningoencephalitis refers to **inflammation of the meninges and brain parenchyma.**

(Ref: Robbins/10th/1261)

Q. What are the degenerative and demyelinating diseases of CNS? *(Important for VIVA)*

Ans.

Demyelinating diseases: Demyelinating diseases of the CNS are acquired conditions characterized by preferential ***damage to myelin*** with relative preservation of axons.

- Multiple sclerosis (MS)
- Neuromyelitis optica
- Acute disseminated encephalomyelitis and acute necrotizing hemorrhagic encephalomyelitis
- Central pontine myelinolysis

(Ref: Robbins/10th/1269)

Degenerative diseases: Neurodegenerative diseases are disorders characterized by the ***progressive loss of particular groups of neurons***, which often have shared functions.

The pathologic process that is common across most of the neurodegenerative diseases is the accumulation of protein aggregates (hence the occasional use of the term "**proteinopathy**").

- Prion Diseases
  - Creutzfeldt-Jakob disease (CJD)
  - Variant Creutzfeldt-Jakob disease
- Alzheimer disease (AD)
- Frontotemporal lobar degenerations (FTLDs)
- Parkinson disease (PD)
- Atypical parkinsonian syndromes
  - Progressive supranuclear palsy (PSP)
  - Corticobasal degeneration (CBD)
  - Multiple system atrophy (MSA)
- Huntington disease (HD)
- Spinocerebellar degenerations
  - Spinocerebellar ataxias (SCA)
  - Friedreich ataxia
  - Ataxia-telangiectasia
- Amyotrophic lateral sclerosis (ALS)
- Other motor neuron diseases
  - Spinal and bulbar muscular atrophy (Kennedy disease)
  - Spinal muscular atrophy (SMA).

(Ref: Robbins/10th/1273)

Q. What are the causes of intracranial hemorrhage?

Ans.

Intracranial hemorrhage:

1. **Traumatic lesion**
2. **Non-traumatic:**
   - Hypertension
   - Cerebral amyloid angiopathy (CAA)
   - Systemic coagulation disorder
   - Neoplasms
   - Vasculitis
   - Aneurisms
   - Vascular malformations (arteriovenous malformations, cavernous malformations, capillary telangiectasias, and venous angiomas).

(Ref: Robbins/10th/1257)

Tumors of CNS

Tumours of the CNS may originate in the brain or spinal cord (**primary tumours**), or may spread to the brain from another primary site of cancer (**metastatic tumours**). Primary CNS tumours or intracranial tumours include: tumours arising from *constituent cells of the brain* (with the sole exception of microglial cells) and from *the supporting tissues.*

(Ref: Harsh Mohan/7th/878)

Q. Classify tumours of CNS. (RMU-21/19/17M,11Ju,08Ja)
Q. Classify brain tumours. (CMU-23M)
Q. Write down the name of malignant tumours of CNS. (RMU-22M)
Q. Classify major classes of brain tumours. (CU-10Ja)
Q. What are the primary brain tumours?
Ans.

Tumors of CNS: ***(Very Important for VIVA)***

1. **Tumours of neuroglia (Gliomas):**
   - Astrocytoma
   - Oligodendroglioma
   - Ependymoma
2. **Tumours of neurons (Neuronal tumors):**
   - Neuroblastoma
   - Ganglioneuroblastoma
   - Ganglioneuroma
3. **Poorly differentiated and embryonal tumours:**
   - Medulloblastoma
   - Neuroblastoma
4. **Tumours of meninges:**
   - Meningiomas
   - Meningeal sarcoma
5. **Peripheral nerve sheath tumours:**
   - Schwannoma (neurilemmoma)
   - Neurofibroma
   - Malignant peripheral nerve sheath tumour
5. **Other parenchymal tumors:**
   - Primary CNS lymphoma
   - Germ cell tumors
   - Pineal parenchymal tumors
6. **Miscellaneous tumours:**
   - Malignant melanoma
   - Craniopharyngioma
   - Pineal cell tumours
   - Pituitary tumours
7. **Familial tumor syndromes:**
   - Neurofibromatosis type-1
   - Neurofibromatosis type-2
   - Tuberous sclerosis
8. **Metastatic tumors** (*more common than primary intracranial neoplasms*)**:** From carcinomas of the lung, breast, skin (malignant melanoma), kidney, gastrointestinal tract and choriocarcinoma. Infiltration from lymphoma and leukaemias may also occur.

(Ref: Robbins/10th/1241,1293; Harsh Mohan/7th/878,883)

Nice to Know:

Metastatic tumour deposits in the brain are commonly multiple, well-defined and usually located at the grey and white matter junction.

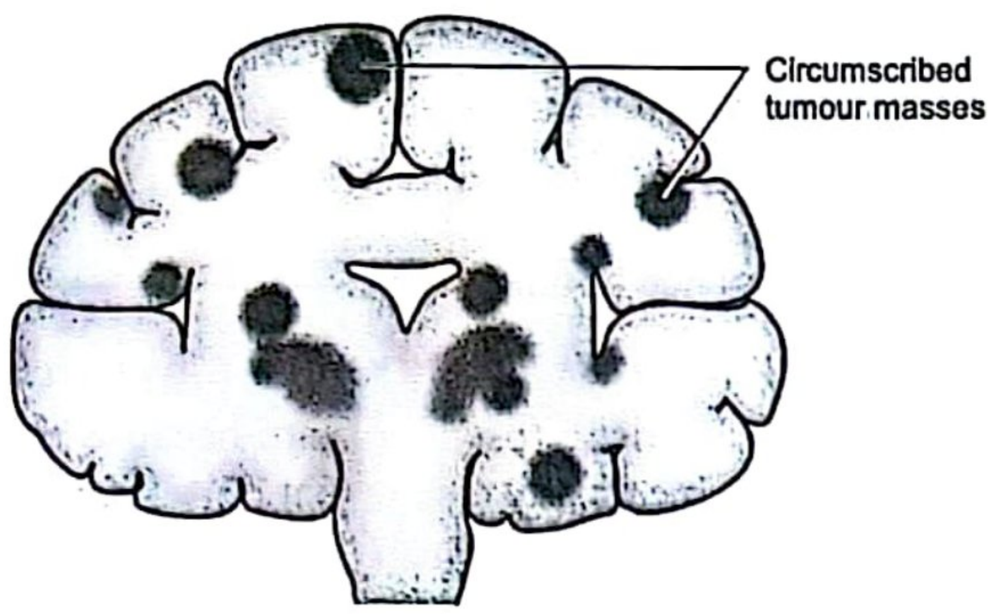


Fig: Metastatic tumour deposits in the brain.

(Ref: Harsh Mohan/7th/884)

Q. What are the special characteristics of CNS tumors / brain tumours? (CMU-21Nv,20Nv/M,19/18/17M,14Ju,10Ja, BUP-22M) ***(Very Important for VIVA)***

Q. Write the peculiarities of CNS tumors. (DU-23Nv, CU-18Nv)

Q. Mention the differences between tumours of the nervous system and tumours of the other parts of the body.

Ans.

Differences between tumours of the nervous system and tumours of the other parts of the body: Tumours of the nervous system have several unique characteristics that set them apart from neoplastic processes elsewhere in the body.

First, the clinical course of disease is relatively unique in case of brain tumors. Thus, some glial tumors with benign histologic features (low mitotic rate, cellular uniformity, and slow growth) may infiltrate large regions of the brain and lead to serious clinical deficits and poor prognosis.

Second, because of their infiltrative behavior, it is often not feasible to resect glial neoplasms completely without compromising neurologic function.

Third, any neoplasm can have lethal consequences if it is located in a critical region, as when a benign meningioma, by compressing the medulla, causes cardiorespiratory arrest.

Finally, the pattern of the spread of primary CNS neoplasms differs from that of other tumours: even the most highly malignant gliomas rarely metastasize outside the CNS.

(Ref: Robbins/10th/1293 + 8th/1330)

Q. Mention the types of astrocytoma. ***(Very Important for VIVA)***

Q. Short note: Glioma. (CU-19Nv)

Ans.

Glioma: Gliomas is the most common group of **primary brain tumors** including ***astrocytomas***, ***oligodendrogliomas***, and ***ependymomas***.

Astrocytoma: Most common primary brain tumours. They can be divided based on their infiltration into the surrounding brain parenchyma.

1. **Infiltrating astrocytomas**
   - Diffuse astrocytoma
   - Anaplastic astrocytoma
   - Glioblastoma multiforme

2. **Non-infiltrating astrocytomas**
   - Pilocytic astrocytoma
   - Pleomorphic xanthoastrocytoma
   - Brainstem glioma.

Oligodendroglioma: Malignant tumor of ***oligodendrocytes***.

- Calcified tumor often involving ***frontal lobe***
- May present as ***seizures***
- Histology shows **'fired egg'** appearance of tumor cells.

Ependymoma: Malignant tumor of ***ependymal cells*** usually seen in ***4th ventricle***.

- Perivascular ***pseudorosette*** is characteristic (pseudorosette because the central structure isn't part of the tumor. Originally, pseudorosette meant any rosette that didn't have a truly empty lumen).
- Tumor can result in ***hydrocephalous***.

(Ref: Robbins/10th/1293; BRS Pathology/5th/383; Pathoma Lecture Notes)

Q. Short note: Oligodendroglioma.

Ans.

Oligodendroglioma: These are malignant tumors of ***oligodendrocytes***, presents as ***slow-growing tumor*** in the ***middle-age group*** often involving ***frontal lobe*** of ***cerebral hemisphere.*** May present as ***seizures***.

Morphology:

***Gross*:**

- Infiltrative tumors that form gelatinous, gray masses, and may show cysts, focal hemorrhage, and calcification.

***Microscopic*:**

- Closely packed cells with large round nuclei surrounded by a clear halo of cytoplasm (**"fried egg"** appearance).
- Tumor divided into groups of cells by delicate capillary strands.
- Foci of calcification (presents in 90% of cases).

(Ref: Robbins/10th/1295; BRS Pathology/5th/384; Pathoma Lecture Notes)

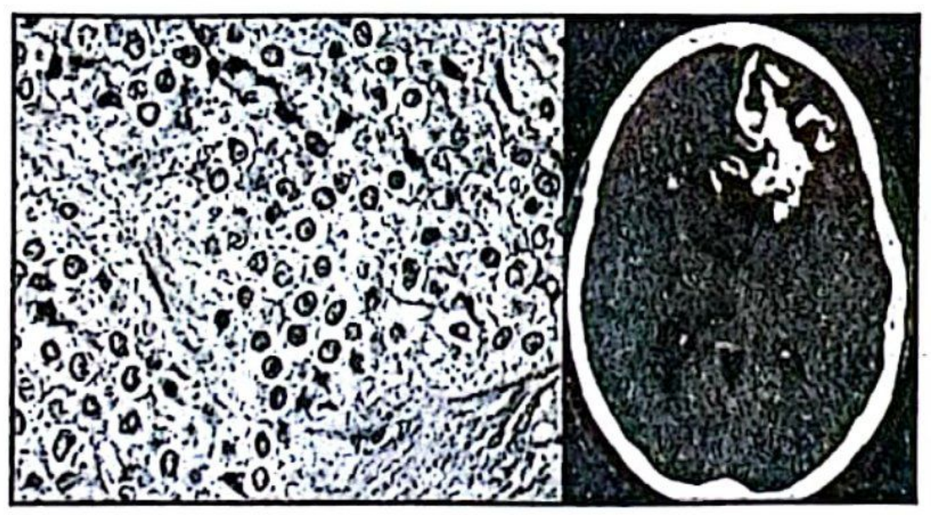


Fig: Histology shows 'fired egg' appearance of tumor cells (left); Calcified tumor involving frontal lobe (right).

Q. Short note: Meningioma. (DU-07Ja, SU-12Ju, CU-12Ja)

Ans.

Meningioma: This is the **second most common primary intracranial neoplasm**. Most cases are **benign** and **slow growing**. The neoplasm originates in **arachnoidal cells of the meninges**; it is **external to the brain** and can often be **successfully removed surgically.** It can cause **seizure** by compression.

They are uncommon in children (most often occurs after 30 years of age) and show a moderate (3:2) female predominance.

Molecular genetics: Many show deletion, loss, or mutation in the *NF2* locus.

Common sites of involvement:

- Convexities of the cerebral hemispheres
- Dura over the lateral convexity
- Wing of the sphenoid
- Olfactory groove
- Sella turcica
- Foramen magnum.

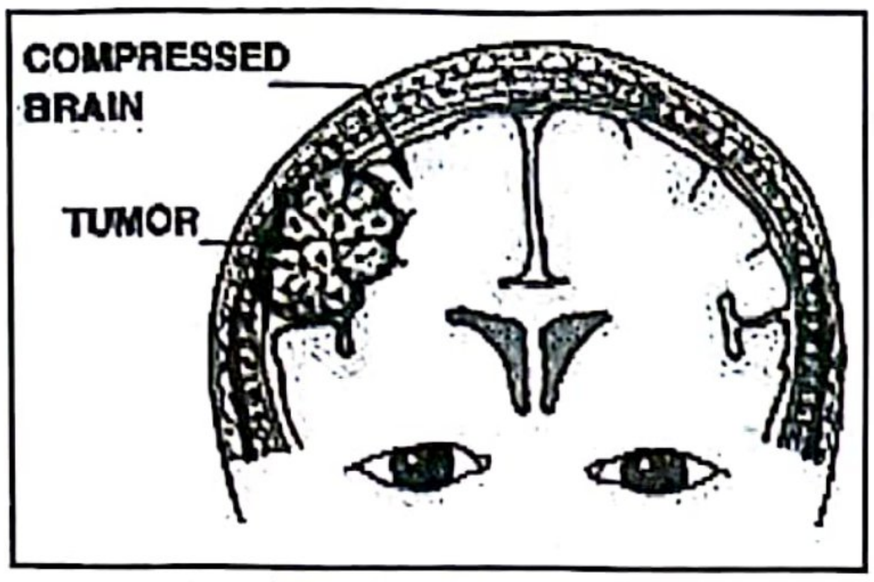


Fig: Meningioma (right).

Morphology:

***Gross*:**

- Usually **rounded masses** with well defined dural bases that **compress underlying brain** but are easily separated from it.
- Extension into the overlying bone may be present.
- Usually **encapsulated** with thin, fibrous tissue.

***Histological*:**

- **Whorled pattern** of concentrically arranged spindle cells
- Laminated calcified **Psammoma bodies** may be present.

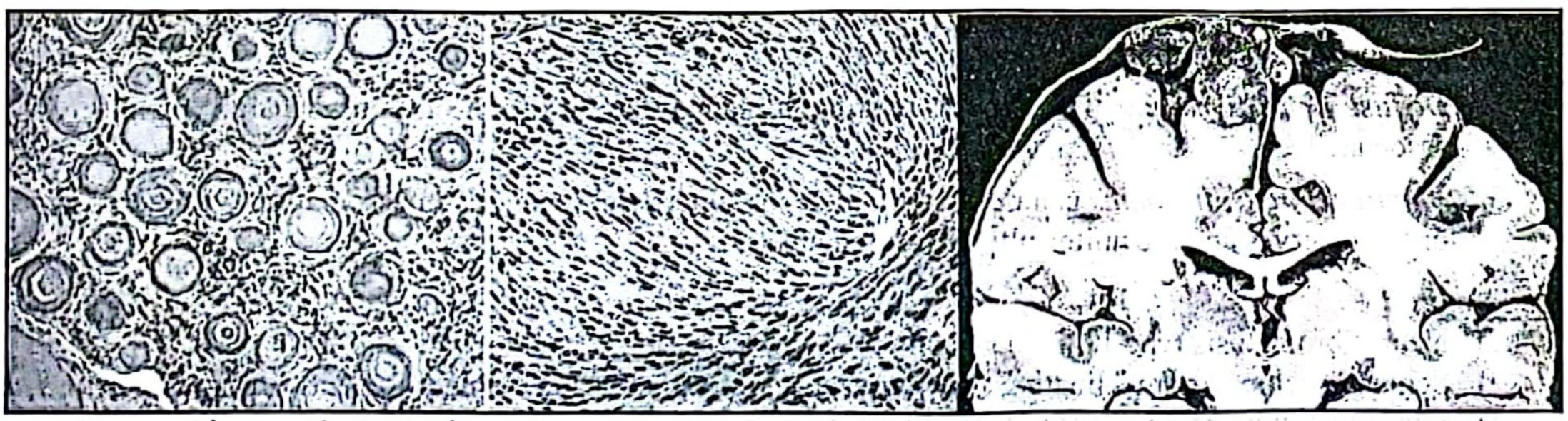


Fig: psammoma bodies (left); cellular whorls (middle); gross (right).
(Ref: Robbins/10th/1300; BRS Pathology/5th/384; Pathoma Lecture Notes)

Q. Short note: Peripheral nerve sheath tumours. (CU-16Ju)

Ans.

Peripheral nerve sheath tumours: A number of benign and malignant neoplasms are grouped together as peripheral nerve sheath tumors—all likely arise from cells of ***Schwann cell lineage.***

The **three** common peripheral nerve sheath tumors:

1. **Schwannoma:** This benign, slowly growing encapsulated tumor arises from Schwann cells.
2. **Neurofibroma:** This neoplasm occurs as solitary or multiple tumors of peripheral nerves derived from Schwann cells that can be subtyped as localized cutaneous, diffuse, or plexiform.

3. **Malignant peripheral nerve sheath tumor (MPNST):** Most (approximately 85%) are high-grade tumors, but low-grade variants are recognized. About half arise in NF1 patients and are assumed to result from malignant transformation of a plexiform neurofibroma.

Peripheral nerve sheath tumors have association with relatively common **familial tumor syndromes**, including neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), and schwannomatosis.

(Ref: Robbins/10th/1236; BRS Pathology/5th/385)

Q. Short note: Schwannoma. (CMU-23M,13Ju)

Ans.

Schwannoma: It is a benign tumour that exhibits **Schwann cell differentiation** and often arises directly from peripheral nerves. Schwannomas are a component of NF_2.

Morphology:

- Schwannomas are **well-circumscribed, encapsulated masses** that abut the associated nerve without invading it, a feature that simplifies surgical excision.
- **Grossly,** these tumours form **firm, gray masses.**
- **Microscopically,** they are comprised of an **admixture of dense and loose areas** referred to as **Antoni-A** and **Antoni-B** areas, respectively.

(Ref: Robbins/10th/1237)

Q. Write in brief about neurofibroma. (CU-20/13Ju)

Q. Short note: Neurofibroma. (CMU-21M,20Nv)

Ans.

Neurofibroma: A neurofibroma is a **benign nerve sheath tumor** in the peripheral nervous system.

Origin: Neurofibromas arise from nonmyelinating-type **Schwann cells.**

The neoplastic Schwann cells are admixed with perineurial-like cells, fibroblasts, mast cells, and CD34+ spindle cells. Neurofibromas may be either sporadic or NF1-associated.

Sub-types: Different types of neurofibroma can be distinguished depending on their growth pattern-

1. ***Superficial cutaneous neurofibromas*** often present as pedunculated nodules that can be seen isolated (if sporadic) or multiple (if NF1-associated).
2. ***Diffuse neurofibromas*** often present as a large plaque-like elevation of skin and are typically NF1-associated.
3. ***Plexiform neurofibromas*** can be found in deep or superficial locations in association with nerve roots or large nerves and are uniformly NF1-associated.

Aetiology:

1) Neurofibromatosis type 1 (NF1) gene.
2) Schwann cells: Non-myelinating Schwann cells are the neoplastic element in neurofibromas.
3) Loss of heterozygosity leads to loss of tumor suppressor function leads to neurofibroma formation.

(Ref: Robbins/10th/1237)

Q. State the difference between Schwannoma and neurofibroma. (CMU-22M,20M)

Ans.

Difference between Schwannoma and neurofibroma:

Traits	Schwannoma	Neurofibroma
1. Location	Cerebellopontine angle (vestibular branch of 8th nerve); extradural sites	Dermis; along the nerve trunk
2. Number	Generally solitary	Solitary or multiple neurofibromatosis
3. Genetics	Bilateral in association with type 2	Multiple associated with type 1

	neurofibromatosis having autosomal dominant inheritance (chromosome 22 disorder)	neurofibromatosis having autosomal dominant inheritance (chromosome 17 disorder)
4. Gross appearance	Firm, encapsulated, c/s tan, translucent	Soft, well demarcated but unencapsulated, c/s mucoid, translucent
5. Microscopy	Compact areas (Antoni A) and myxomatous areas (Antoni B), palisading tumour cells (Verocay bodies)	Dense collagen fibres and abundant extracellular mucoid material
6. Infiltration	Encapsulated along the edge of nerve without invading it	May infiltrate the peripheral nerve
7. Immunohistochemistry	S-100 protein	EMA; sometimes S-100 protein
8. Behaviour	Invariably benign	May turn malignant

(Ref: Harsh Mohan/7th/887)

CHAPTER 17

THE EYE

Q. What are the conjunctival and corneal diseases?
Ans.
Conjunctival diseases:

a) Conjunctival scarring
b) Pinguecula and pterygium
c) **Neoplasms**
   - Conjunctival squamous cell carcinoma
   - Conjunctival intra-epithelial neoplasia (CIN)
   - Mucoepidermoid carcinoma
   - Conjunctival nevi
   - Conjunctival melanoma.

(Ref: Robbins/10th/1310)

Corneal diseases:

a) Keratitis and ulcers
b) Corneal degenerations and dystrophies
   - Band keratopathies
   - Keratoconus
   - Fuchs endothelial dystrophy
   - Stromal dystrophies.

(Ref: Robbins/10th/1311)

Q. What are the neoplasms of the orbit? *(Important for VIVA)*
Ans.
Neoplasms of the orbit:

1. **Primary neoplasms:**
   - Capillary hemangioma (infancy and early childhood)
   - Lymphangioma
   - Cavernous hemangioma (adults)
   - Pleomorphic adenoma of the lacrimal gland
   - Dermoid cyst

- Neurilemmoma
- Orbital lymphomas (Non-Hodgkin lymphoma)

2. **Secondary (metastatic) neoplasms:**
   - Metastatic prostatic carcinoma
   - Metastatic neuroblastoma
   - Metastatic Wilms tumor.

(Ref: Robbins/10th/1307)

Q. What are the common malignancies of the eyelid? ***(Important for VIVA)***

Ans.

Common malignancies of the eyelid:

1. Basal cell carcinoma
2. Sebaceous carcinoma.

(Ref: Robbins/10th/1308)

Q. What are the common retinal diseases?

Ans.

Common retinal diseases:

1. Retinal detachment
2. Retinal vascular disease
   - Hypertensive retinopathy
   - Diabetic retinopathy
   - Retinopathy of prematurity
   - Radiation retinopathy
   - Retinal vasculitis
   - Sickleretinopathy
   - Retinal artery and vein occlution.
3. Age related macular degeneration
4. Retinitis pigmentosa
5. Retinitis due to *candida* infection
6. Retinal neoplasms
   - Retinoblastoma
   - Retinal lymphoma.

(Ref: Robbins/10th/1319)

Q. Short note: Retinoblastoma. (SU-17M)

Ans.

Retinoblastoma: It is the ***most common*** primary intraocular malignancy of children.

Age: Diagnosed usually prior to the 4 years of age.

Pathogenesis of retinoblastoma: Two mutations of the **RB gene,** located on chromosome **13q14** lead to neoplastic proliferation of the retinal cells. ***(Important for VIVA)***

Morphology:

1. The pathology of retinoblastoma of both hereditary and sporadic type is identical.
2. Tumours may contain both undifferentiated and differentiated elements.
3. Undifferentiated elements appear as collections of small round cells with hyperchromatic nuclei.
4. Viable tumour cells are found encircling tumour blood vessels with zones of necrosis typically found in relatively avscular areas.
5. Focal zones of dystrophic calcification are characteristic of retinoblastoma.

(Ref: Robbins/10th/1324)

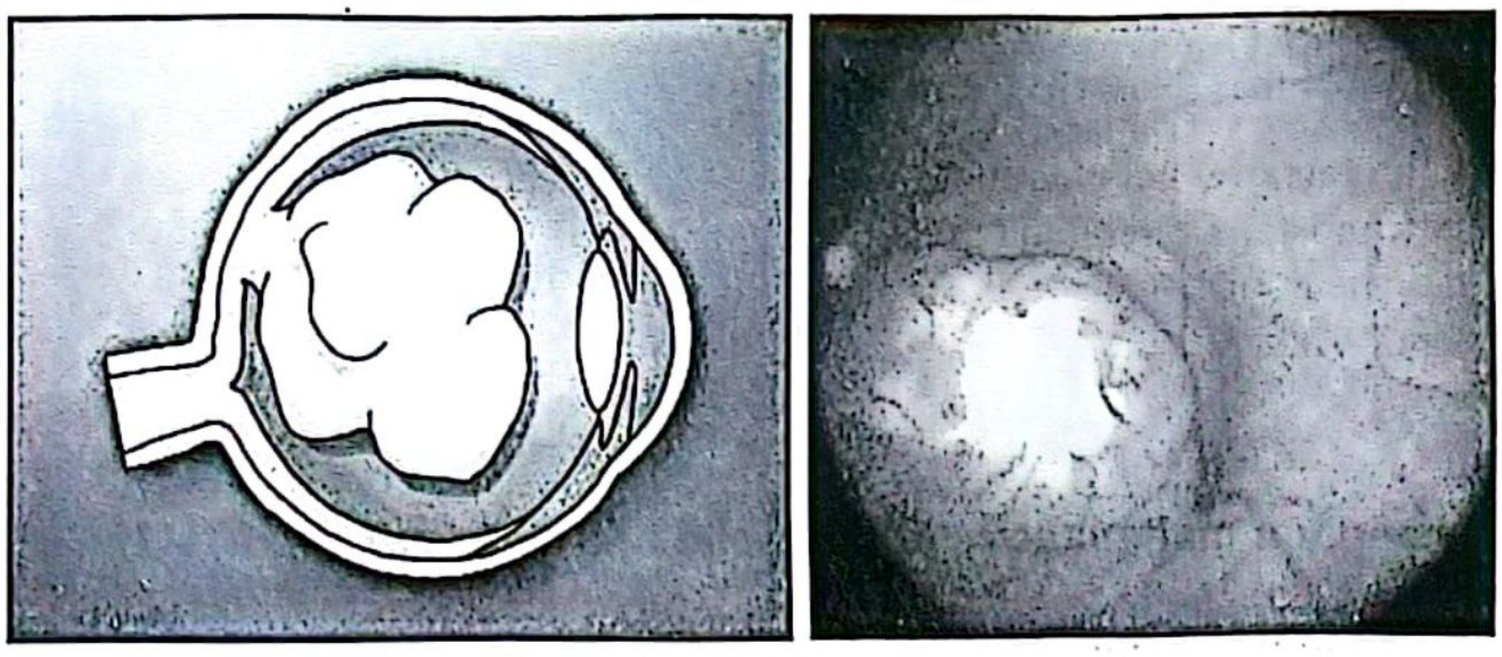


Fig: Retinoblastoma.

Q. Short note: Cataract.

Ans.

Cataract: The term **cataract** describes ***lenticular opacities*** that may be congenital or acquired.

Causes of cataract:

1. Congenital
2. Acquired
   - Galactosemia
   - Diabetes mellitus
   - Wilson's disease
   - Atopic dermatitis
   - Drugs (especially corticosteroids)
   - Radiation
   - Trauma
   - Age related- nuclear sclerosis.

(Ref: Robbins/10th/1313)

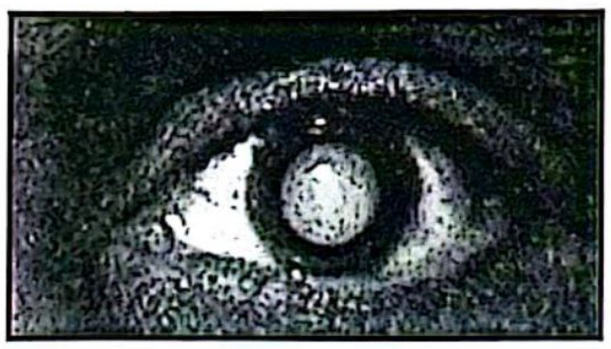


Fig: Cataract.

Q. Short note: Glucoma.

Ans.

Glucoma: The term **glucoma** refers to a collection of diseases characterized by distinctive changes in the visual field and in the cup of the optic nerve. Most of the glucomas are associated with ***elevated intra-occular pressure.***

Classification of glucoma:

1. ***Primary***:
   - Primary open angle glucoma (most common)
   - Primary angle closure glucoma
2. ***Secondary***:
   - Secondary open angle glucoma
   - Secondary angle closure glucoma.

(Ref: Robbins/10th/1314)

MCQ of Systemic Pathology

e) pericarditis (F)

Q. Complications of rheumatic heart disease are - (DU-11Ja)
a) Systemic hypertension (F)
b) Pulmonary valve deformity (T)
c) Ventricular tachycardia (F)
d) Pancarditis (T)
e) Mural thrombus (T)

Q. Hypertensive heart disease include - (DU-10Ja,09Ju)
a) Left ventricular hypertrophy (T)
b) Right ventricular hypertrophy (T)
c) Cor-pulmonale (F)
d) Acute myocardial infarction (F)
e) Ventricular tachycardia (T)

Lymph Nodes

Q. Causes of generalized lymphadenopathy: (DU-23Nv)
a) Tubercular infection (T)
b) SLE (T)
c) Coxsackie viral infection (F)
d) Aspergillus fungal infection (F)
e) Lipid storage disease (F)

Q. Features of chronic non-specific lymphadenitis are- (CMU-22M)
a) Follicular hyperplasia (T)
b) Follicular atrophy (F)
c) Paracortical hyperplasia (F)
d) Nodular sclerosis (F)
e) Sinus histocytosis (T)

Q. Reed-Sternberg (RS) cells are- (RMU-22M)
a) Tumour giant cell (T)
b) Inflammatory giant cells (F)
c) Found in non-Hodgkin lymphoma (F)
d) Found in Hodgkin lymphoma (T)
e) May be multilobed nuclei present (T)

Q. Features of Hodgkin's lymphoma includes- (DU-19Nv)
a) Presence of monomorphic cell population (F)
b) Presence of R-S cells (T)
c) Los of nodal architecture (F)
d) Noncontiguous spread (F)
e) Extra-nodal tissue involvement (T)

Q. Subtypes of Hodgkin's lymphoma are- (CU-19Nv)
a) Nodular fascitis (F)
b) Lymphocyte-poor (F)
c) Lymphocyte-depletion (T)
d) Lymphocyte-rich (T)
e) Mixed cellularity (T)

Q. Hodgkin's lymphoma- (DU-18M)
a) R-S cell or variants are always present (T)
b) Non-contagious spread (F)
c) Mesenteric lymph nodes are usually involved (F)
d) Involvement of both sides of diaphragm means higher stage (T)
e) Extranodal involvement is common (F)

Q. Character of RS cell - (RU-18M)
a) Large cell about 15-45 μm diameter (T)
b) Comes from T lymphocyte (F)
c) Comes from B lymphocyte (T)
d) Abundant amphophilic cytoplasm (F)
e) Usually found in Non-Hodgkins lymphoma (F)

Q. Followings are features of Hodgkin's lymphoma- (DU-18Ja)
a) Polymorphous cell population (T)
b) Presence of RS type of giant cell (T)
c) Contageous lymphnode involvement (T)
d) Monomorphic cell population (F)
e) Walder's ring involved (F)

Q. Features of Hodgkin lymphoma include - (DU-17Nv)
a) Presence of Langhans type of giant cell (F)
b) Giant cell is the neoplastic element (F)
c) Contiguous spread (T)
d) T cell neoplasm (F)
e) Extra-nodal presentation is common (F)

Q. Non-Hodgkin lymphoma- (DU-17M)
a) Usually involves single group of lymph nodes (F)
b) Usually has non-contagious spread (T)
c) Does not involve spleen or mesenteric lymph nodes (F)
d) Is characterized by effacement of nodal architecture of lymph nodes (F)
e) Can occur in GIT (T)

Q. Clinical features of Hodgkin's disease- (RU-17M)

MCQ of Systemic Pathology

Blood Vessels

Q. Risk factors of atherosclerosis include- (DU-23M)
a) Hypercalcemia (F)
b) Hyperlipidemia (T)
c) Hypertension (T)
d) Obesity (T)
e) Increased work load (F)

Q. Risk factors of atherosclerosis are: (RMU-22M)
a) High HDL level (F)
b) Smoking (T)
c) Intake of antioxidant (F)
d) Eating saturated fat (T)
e) Sedentary lifestyle (T)

Q. Major modifiable risk factors for atherosclerosis include: (DU-21Oct/M)
a) Obesity (F)
b) Diabetes mellitus (T)
c) Alcohol drink (F)
d) High carbohydrate diet (F)
e) Cigarette smoking (T)

Q. Risk factors affecting atherosclerosis are: (DU-19Nv)
a) Increased HDL level (F)
b) Homocystenemia (T)
c) Intake of anti-oxidant (F)
d) Intake of saturated fatty acid (T)
e) Type A personality (T)

Q. Complications of atheromatous lesion includes (DU-18Ja)
a) Intraplaque hemorrhage (T)
b) Thrombus formation (T)
c) Cyst formation (F)
d) Dystrophic calcification (T)
e) Intraplaque granuloma (F)

Q. Pulmonary embolism is associated with - (DU-17Ja)
a) thrombosis in pulmonary vein (F)
b) thrombosis in calf vein (T)
c) thrombosis in pelvic vein (F)
d) thrombosis in left heart (F)
e) thrombosis in pulmonary trunk (F)

Q. Risk factors for atherosclerosis include: (DU-15Ju)
a) Hyperlipidaemia (T)
b) Hypercalcaemia (F)
c) Obesity (T)
d) Hypertension (T)
e) Hypercagulability (F)

Q. In myocardial infarction - (DU-14Ja)
a) There is leukocytosis (T)
b) Troponin-I is raised on the very first day (T)
c) Creatinine kinase appears earlier than troponin-I (F)
d) There may not be ECG change in first two hours (T)
e) All the enzymes should be tested after 7 days (F)

Q. Risk factors for atherosclerosis are - (DU-13Ja)
a) Diabetes mellitus (T)
b) Homocystinuria (F)
c) Lysosomal storage disease (F)
d) Alcohol intake (T)
e) Partial gastrectomy (F)

Q. Complications of atherosclerosis include - (DU-11Ju)
a) fissuring of the lesion (T)
b) calcification (T)
c) malignant transformation (F)
d) ossification (F)
e) haemorrhage (T)

Q. Foam cells in atheroma are derived from - (DU-10Ju)
a) Endothelial cell (F)
b) Monocyte (T)
c) Histiocyte (T)
d) Smooth muscle (T)
e) Neutrophil (F)

Q. Following may lead to secondary hypertension - (DU-09Ja)
a) Hypothyroidism (F)
b) Hyperaldosteronism (T)
c) Addison's disease (F)
d) Pheochromocytoma (T)
e) Renal artery stenosis (T)

The Heart

Q. Major criteria of rheumatic fever: (DU-23Nv)
a) Pancarditis (T)
b) Raised ASO titer (F)
c) Erythema marginatum (T)

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d) Arthralgia (F)
e) Subcutaneous nodules (T)

Q. Jones criteria include: (BUP-22Nv)
a) Polyarthritis (F)
b) Carditis (F)
c) Sub-cutaneous nodule (T)
d) Arthralgia (T)
e) Fever (T)

Q. Examples of IHD disease: (CMU-22M)
a) Angina pectoris (T)
b) Chronic ischaemic heart disease (T)
c) Infective endocarditis (F)
d) Hypertrophic cardiomyopathy (F)
e) Sudden cardiac death (T)

Q. Components of tetralogy of fallot: (RMU-22M)
a) Left ventricular hypertrophy (F)
b) Right ventricular hypertrophy (T)
c) Ventricular septal defect (T)
d) Atrial septal defect (F)
e) Aortic stenosis (F)

Q. The following changes are observed in acute MI: (DU-21Ja,20Nv/M)
a) Raised troponin-I (T)
b) Raised serum creatinine (F)
c) Leukopenia (F)
d) Blood cholesterol level above 200 mg/dl (F)
e) Lactate dehydrogenase (T)

Q. Following are markers for IHD: (CU-19Nv)
a) CK-MB (T)
b) LDH (T)
c) ALT (F)
d) AST (T)
e) Troponin-I (T)

Q. Diagnostic markers of MI are: (DU-18M)
a) CPK (T)
b) ALT (F)
c) AST (T)
d) Troponin-I (T)
e) Acid phosphatase (F)

Q. Enzymes of clinical importance in myocardial infarction - (DU-17Nv)
a) Serum amylase (F)
b) CPK (T)
c) Pyruvate kinase (F)
d) Lactate dehydrogense (T)
e) Aspartate aminotransferase (T)

Q. Regarding rheumatic fever: (DU-17M)
a) Usually has a history of sore throat by group-A β-hemolytic streptococcus (T)
b) Is associated with rheumatoid arthritis (F)
c) Is a late complication of congenital heart disease (F)
d) Is more common in children (T)
e) Is the most frequent cause of mitral stenosis (T)

Q. The following changes are observed in acute MI: (DU-17M)
a) Raised troponin-I (T)
b) Creatine kinase-MM (F)
c) Neutrophilic leukocytosis (T)
d) Blood cholesterol level above 200 mg/dl (F)
e) Raised C-reactive protein (T)

Q. Major criteria of rheumatic heart disease: (DU-15Ju)
a) Raised ASO liter (T)
b) Sydenham chorea (T)
c) Raised ESR (F)
d) Leukocytosis (F)
e) Subcutaneous nodule (T)

Q. The morphological features of acute MI depends on: (DU-15Ju)
a) age of the patient (T)
b) rate of development of coronary obstruction (T)
c) sex of the patient (F)
d) extent of the collateral circulation (F)
e) duration of occlusion (T)

Q. Following are associated with rheumatic fever - (RU-13Ja)
a) High ESR (T)
b) Aschoff body giant cells (T)
c) Genetic predisposition (F)
d) Leukopenia (F)
e) Carditis due to bacterial invasion (T)

Q. Myocardial infarction is associated with - (DU-12Ju)
a) fibrinoid necrosis of myocardium (F)
b) raised level of LDH enzyme (T)
c) ventricular aneurysm (T)
d) leukocytosis (T)
e) myocarditis (F)

Q. Complications of MI includes - (DU-11Ju)
a) rheumatic heart disease (F)
b) contractile dysfunction (T)
c) myxoma (F)
d) myocardial rupture (T)

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a) Multiple peripheral lymph nodes are involved (F)
b) Night sweat (T)
c) Pruritus (F)
d) Extranodal involvement is common (F)
e) Non contiguous spread (F)

Q. Hodgkin lymphoma is characterized by the following features- (DU-17Ja)
a) non-contiguous spread (F)
b) mesenteric nodes are usually involved (F)
c) extra nodal presentation is common (F)
d) popcorn cells are sometimes present (T)
e) nodal architecture is not preserved (T)

Q. Hodgkin's lymphoma shows: (DU-15Ja)
a) Monomorphic cell population (T)
b) Many eosinophil (T)
c) Well preserved nodal architecture (F)
d) Non-contagious spread (F)
e) Rare extranodal tissue involvement (T)

Q. Burkitt lymphoma - (DU-13Ju)
a) Is a T-cell lymphoma (F)
b) Occurs mainly in children and young adult (T)
c) Can be endemic (T)
d) Appears as mass involving mandible if of sporadic type (F)
e) Is very aggressive (T)

Q. The following are correctly matched - (RU-13Ju)
a) Reed-Sternberg cell – non-Hodgkin lymphoma (F)
b) Polycythemia – renal cell carcinoma (T)
c) Saddle thrombus – myocardial infarction (F)
d) Increased albumin-globulin ratio – cirrhosis of liver (F)
e) Necrotizing inflammation – bronchiectasis (T)

Respiratory System

Q. Complications of acute lobar pneumonia include: (DU-23M)
a) Lung abscess (T)
b) Septicemia (T)
c) Interstitial fibrosis (F)
d) Bronchogenic carcinoma (F)
e) Emphysema (F)

Q. Regarding pneumonia: (DU-22Nv)
a) Consolidation (T)
b) Evening rise of temperature (F)
c) Mycoplasma pneumonia (T)
d) Sputum rusty in colour (T)
e) Septicaemia (T)

Q. Bronchogenic carcinoma can secrete: (BUP-22Nv)
a) ADH (T)
b) Aldosterone (F)
c) Beta-hCG (F)
d) Calcitonin (T)
e) ACTH (T)

Q. Regarding COPD following statements are true: (DU-22M)
a) Decreased FEV in 1 sec. (T)
b) Causes reduced expansion of lung (F)
c) Cigarette smoking is not associated (F)
d) Causes copious.sputum in emphysema (F)
e) Mucous gland hyperplasia in chronic bronchitis (F)

Q. Types of bronchogenic carcinoma are- (CMU-22M)
a) Squamous cell carcinoma (T)
b) Transitional cell carcinoma (F)
c) Adenocarcinoma (T)
d) Small cell carcionoma (T)
e) Large cell carcinoma (T)

Q. Features of tuberculosis is associated with: (DU-19Nv)
a) Granuloma formation (T)
b) Caseation necrosis (T)
c) Immune mediated inflammation (T)
d) Type II hypersensitivity reaction (F)
e) Dystrophic calcification (F)

Q. Pathological changes of lobar pneumonia are: (CU-19Nv)
a) Stage of congestion (T)
b) Stage of brown hepatization (F)
c) Stage of grey hepatization (T)
d) Stage of consolidation (F)
e) Stage of resolution (T)

Q. Chronic obstructive pulmonary diseases are: (RU-19M)
a) Asthma (T)
b) Pulmonary neoplasms (F)
c) Emphysema (T)
d) Pneumonia (F)
e) Bronchiestasis (T)

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Q. Common sites of tuberculous bacilli infection: (RU-17M)
a) Lymph node (T)
b) Epididymis (F)
c) Cardiac muscle (F)
d) Thyroid gland (F)
e) Pulmonary tissue (T)

Q. Interstitial lung disease include: (DU-15Ju)
a) Bronchiectasis (F)
b) Sarcoidosis (T)
c) Emphsema (F)
d) Aspergillosis (T)
e) Silicosis (T)

Q. Regarding pneumonia - (DU-14Ja)
a) Consolidation occurs in lung (T)
b) Transplant recipient are vulnerable (F)
c) Mycoplasma may cause it (T)
d) Lung abscess is an important complication (T)
e) Sputum is rusty in colour (F)

Q. Followings are associated with pneumonia - (RU-13Ja)
a) Streptococcal pneumonia (T)
b) Lung abscess (T)
c) E. coli (F)
d) Septicemia (T)
e) Bronchial asthma (F)

Q. Emphysema - (DU-11Ja)
a) Is a component of COPD (T)
b) Is related to cigarette smoking (T)
c) Is characterized by copious purulent sputum (F)
d) Complicated by infection is common (T)
e) Is common in al-antitrypsin deficiency (T)

Q. Pulmonary oedema may occur in patient suffering from - (DU-10Ju)
a) Major trauma (F)
b) Plague (F)
c) Right sided heart failure (F)
d) Hypoproteinaemia (T)
e) Nematode infestation (F)

Head, Neck & Oral Cavity

Q. Benign tumours of salivary gland are - (RU-17M)
a) Acinic cell carcinoma (F)
b) Basal cell adenoma (T)
c) Pleomorphic adenoma (T)
d) Squamous cell carcinoma (F)
e) Warthin's tumour (T)

Q. Malignant tumours of salivary gland include - (DU-09Ju)
a) Mucoepidermoid tumour (T)
b) Warthin tumour (F)
c) Acinic cell tumour (T)
d) Adenoid cyst carcinoma (T)
e) Oncocytoma (F)

Gastrointestinal Tract

Q. Characteristics features of Crohn's disease: (DU-23Nv)
a) Transmural epithelium (T)
b) Caseating granuloma (T)
c) Continuous ulcerative lesion (F)
d) Toxic megacolon (F)
e) Fistula formation (T)

Q. Factors associated with gastric carcinoma: (DU-22Nv)
a) *H. pylori* infection (T)
b) High socio-economic status (F)
c) Barren's oesophagus (F)
d) Partial gastrectomy (T)
e) Blood group B (F)

Q. Factors associated with Ca stomach: (BUP-22Nv)
a) Higher socioeconomic status (F)
b) Infection by *H. pylori* (T)
c) Cigarette smoking (T)
d) Lack of fresh fruit & vegetable (T)
e) Partial gastrectomy (F)

Q. Features of Crohn's disease: (DU-22M)
a) Shallow ulcer (F)
b) Skip lesion (T)
c) Transmural involvement (T)
d) Non-caseating granuloma (T)
e) Frequent dysplastic changes of the lining (F)

Q. Ulcers of small intestine are- (CMU-22M)
a) Duodenal ulcer (T)
b) Typhoid ulcer (T)
c) Crohn's disease (T)
d) Ulcerative colitis (F)
e) Amoebic dysentery (F)

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Q. Fate of acute appendicitis are: (RMU-22M)
a) Lymphoma (F)
b) Appendicular lump (T)
c) Appendicular abscess (T)
d) Hepatocellular carcinoma (F)
e) Seminoma (F)

Q. Gastric carcinoma is associated with following conditions: (DU-21Ja,20Nv/M,17M)
a) Persistent infection by *H. pylori* (T)
b) Prolonged intake of aspirin (F)
c) Alcoholism (F)
d) Chronic atrophic gastritis (T)
e) Crohn's disease (F)

Q. Gastric carcinoma has associated with: (CU-19Nv)
a) H. pylori infection(T)
b) Blood group A(T)
c) Nitrites in food preservatives
d) Adenomatous polyps
e) Malabsorption syndrome

Q. Features of Crohn's disease include: (DU-19M)
a) Superficial mucosal ulcer (F)
b) Fistula formation (T)
c) Non-caseating granuloma (T)
d) Toxic megacolon (F)
e) Serositis (T)

Q. Complications of peptic ulcer disease include: (DU-18M)
a) Haematemesis (T)
b) Adenocarcinoma (T)
c) Perforation (T)
d) Profuse vomiting (F)
e) Diarrhea (F)

Q. The following are associated with gastric carcinoma: (RU-18M)
a) Partial gastrectomy (T)
b) Barret's esophagus (T)
c) Refined carbohydrate intake (F)
d) Intake of high fatty diet (F)
e) Positive occult blood test (T)

Q. Characteristics of ulcerative colitis are: (RU-17M)
a) Usually involve the small intestine (F)
b) Inflammation in mucosa and submucosa (F)
c) Skin lesion (F)
d) No granuloma formation (T)
e) Malignant transformation is rare (F)

Q. Complications of peptic ulcer disease are: (DU-17Ja)
a) perforation (T)
b) reflux esophagitis (T)
c) pyloric stenosis (T)
d) diarrhoea (F)
e) haematemesis (T)

Q. Features of Crohn's disease include: (DU-16Ju)
a) Superficial mucosal ulcer (F)
b) Fistula (T)
c) String sing in barium follow-through (T)
d) Increased risk of adenocarcinoma (F)
e) Toxic megacolon (F)

Q. Stress induced ulcer of stomach include: (DU-15Ja)
a) Peptic ulcer disease (F)
b) Ulcer induced by NSAID (F)
c) Gushing ulcer (T)
d) Curling ulcer (T)
e) Ulcer induced by septic shock (T)

Q. The followings are congenital anomalies of GIT: (DU-14Ju)
a) Hirschsprung's disease (T)
b) hypertrophic pyloric stenosis (T)
c) Crohn's disease (F)
d) familial adenomatous polyposis (T)
e) imperforate anus (T)

Q. The following are features of Crohn's disease - (DU-14Ja)
a) Transmural involvement (T)
b) Presence of dysplasia (F)
c) Shallow ulcer (F)
d) Non-caseating granuloma (T)
e) Toxic megacolon (F)

Q. Duodenal ulcer - (RU-14Ja)
a) Less common than gastric ulcer (F)
b) Associated with hypersecretion of gastric acid (T)
c) Are usually multiple (T)
d) Usual site is 2nd and 3rd part of duodenum (F)
e) Usually requires surgical treatment (F)

Q. Crohn's disease has the following features- (DU-13Ja)
a) Shallow ulcer (F)
b) Skip lesion (T)
c) Transmural involvement (T)

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d) Non-caseating granuloma (T)
e) Frequent dysplastic changes of the lining (F)

Q. Following conditions predispose to colonic cancer- (DU-12Ja)
a) villous adenoma (T)
b) juvenile polyp (F)
c) Chron's colitis (T)
d) chronic ischaemic bowel disease (F)
e) familial polyposis (F)

Q. Peptic ulcer- (DU-11Ja)
a) Morphologically is a fungating ulcer (F)
b) Has clean ulcer bed (T)
c) Is a premalignant condition (T)
d) Can complicate with melaena (T)
e) is usually multiple when due to *H. pylori* (F)

Q. The common sites of gut carcinoid tumour include - (DU-10Ja,09Ju/Ja)
a) Appendix (T)
b) Ileum (T)
c) Within the margins of gastrojejunostomy (F)
d) Rectum (T)
e) With Meckel's diverticulum (F)

Q. Ulcerative colitis leads to - (DU-09Ju)
a) Malignancy (T)
b) Bloody diarrhea (T)
c) Toxic mega colon (T)
d) Hose pipe rigidity (T)
e) Skip lesion (F)

Q. Factors associated with increased incidence of gastric carcinoma include - (DU-08Ju)
a) Infection by H. pylori (T)
b) Higher socioeconomic status (F)
c) Barrett esophagus (T)
d) Partial gastrectomy (T)
e) Cigarette smoking (T)

Liver & Biliary Tract

Q. Causes of chronic liver disease- (DU-23M)
a) hepatitis A virus (F)
b) hepatitis B virus (T)
c) hepatitis C virus (T)
d) human papilloma virus (F)
e) hepatitis E virus (F)

Q. Liver cirrhosis is associated with: (DU-22M)
a) Splenomegaly (T)
b) Haemorrhoids (T)
c) Normal PT (F)
d) Spider angioma (T)
e) Proteinuria (T)

Q. Complications of gallstone- (RMU-22M)
a) Empyema of the gall bladder (T)
b) Carcinoma of the gall bladder (T)
c) Liver failure (F)
d) Renal failure (F)
e) Cirrhosis of liver (F)

Q. The following conditions predispose gall stone formation- (DU-21Ja,20Nv/M,17M)
a) Viral hepatitis (F)
b) Cirrhosis of liver (F)
c) Hereditary spherocytosis (T)
d) Obesity (T)
e) Raised serum TG (T)

Q. Complication of cirrhosis of liver include - (DU-21Ja,20Nv/M,17Nv)
a) Hepatocellular carcinoma (T)
b) Ascites (T)
c) Haematemesis and melena (T)
d) Testicular atrophy (F)
e) Hyperlipidaemia (F)

Q. Consequences of portal hypertension- (DU-19M)
a) Esophageal varices (T)
b) Ascites (T)
c) Increased bilirubin (F)
d) Caput medusa (T)
e) Congestive splenomegally (T)

Q. Hepatitis-C virus is associated with- (DU-18M)
a) Chronic hepatitis (T)
b) Ground glass hepatocyte (F)
c) Fatty change in hepatocytes (T)
d) Neutrophils in portal triad (F)
e) Faecal-oral transmission (F)

Q. Followings are associated with cirrhosis of liver- (RU-18M)
a) Disorganization of hepatic architecture (T)
b) Localized edema (F)
c) Iron overload (F)
d) Portal hypotension (F)
e) Enlarged liver (T)

Q. Risk factors for gall stone formation- (RU-17M)
a) Reproductive age of female (T)

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b) Old age of female (F)
c) Rapid weight reduction (T)
d) Obesity (T)
e) Hepatitis (F)

Q. Major consequences of portal hypertension are- (DU-17Ja)
a) hepatic encephalopathy (T)
b) ascites (T)
c) increased bilirubin & bile formation (F)
d) formation of portosystemic venous shunt (T)
e) congestive splenomegaly (T)

Q. Portal hypertension is related to- (DU-16Ju)
a) Ascites (T)
b) Opening of porto-caval anastomosis (T)
c) Splenic fibrosis (F)
d) Portal vein thrombosis (F)
e) Encephalopathy (T)

Q. Etiological factors relevant to hepatocellular carcinoma are: (DU-16Ja)
a) viral infection (T)
b) tobacco smoking (F)
c) chronic alcoholism (T)
d) helicobacter pylori infection (F)
e) exposure to aflatoxin (T)

Q. Hepatitis A virus can produce: (DU-15Ju)
a) Haemolytic jaundice (F)
b) Acute hepatitis (T)
c) Chronic hepatitis (F)
d) Fulminant hepatitis (T)
e) Carrier state (F)

Q. Morphology of acute hepatitis include: (DU-14Ju)
a) balooning degeneration (F)
b) bile duct proliferation (F)
c) bridging necrosis (T)
d) portal tract infiltration (T)
e) fibrosis (T)

Q. Features of portal hypertension - (RU-14Ja)
a) ascites (T)
b) oesophageal varices (T)
c) splenomegally (T)
d) hemorrhoids (T)
e) caput medusa in anterior abdominal wall (T)

Q. Causes of hepatocellular carcinoma include - (RU-14Ja)
a) Leishmania Donnovani (F)
b) HCV (T)
c) HAV (F)
d) Aflatoxin (T)
e) Chronic alcoholism (T)

Q. In chronic liver disease - (DU-13Ju)
a) Prothrombin time is prolonged (T)
b) Serum bilirubin is always raised (F)
c) Serum alkaline phosphatase is raised (F)
d) A:G ratio is altered (T)
e) Clotting time can be increased (T)

Q. Gall stones are associated with - (DU-13Ju)
a) viral hepatitis (F)
b) cirrhosis of liver (F)
c) hereditary spherocytosis (T)
d) obesity (T)
e) raised serum triglyceride (F)

Q. Obstruction of common bile duct is associated with - (DU-13Ju)
a) a great increase in alkaline phosphatase (T)
b) an increase in serum concentration of unconjugated bilirubin (F)
c) a decrease in fecal stercobilinogen content (T)
d) an increase in fecal fat (T)
e) an increase in urinary urobilinogen (F)

Q. The following are associated with carcinoma liver - (RU-13Ju)
a) Hepatitis C virus (T)
b) Beta naphylamine (F)
c) aflatoxin (T)
d) EBV (F)
e) Schistosoma haematobium (F)

Q. Decreased albumin-globulin ratio found in - (RU-13Ju)
a) Nephritic syndrome (T)
b) lymphoma (F)
c) cirrhosis of liver (T)
d) xeroderma pigmentosa (F)
e) Cystitis (F)

Q. Major consequences of portal hypertension are - (DU-12Ju)
a) hepatic encephalopathy (T)
b) ascites (T)
c) increased bilirubin and bile formation (F)
d) formation of porto-systemic shunt (T)
e) splenic atrophy (F)

Q. Following are raised in chronic liver disease - (DU-11Ju)

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a) bleeding time (F)
b) clotting time (T)
c) serum bilirubin (T)
d) prothrombin time (T)
e) serum albumin (F)

Q. Gall stones are associated with - (DU-10Ja)
a) Viral hepatitis (F)
b) Cirrhosis of liver (F)
c) Hereditary spherocytosis (T)
d) Obesity (T)
e) Sickle cell anaemia (T)

Q. Gall stones are associated with - (DU-09Ju)
a) Viral hepatitis (F)
b) Cirrhosis of liver (F)
c) Hereditary spherocytosis (T)
d) Obesity (T)
e) Raised serum triglycerides (F)

Pancreas

Q. Causes of acute pancreatitis include - (DU-10Ju)
a) Measles (F)
b) Hyperthermia (F)
c) Choledocholithiasis (T)
d) Azathioprine therapy (F)
e) Alcohol abuse (T)

Renal System

Q. Urinary findings of nephrotic syndrome are- (DU-23M)
a) RBC cast (F)
b) pyuria (F)
c) lipiduria (F)
d) massive proteinuria (T)
e) hyaline cast (T)

Q. Manifestations of AGN are- (RMU-22M)
a) Hematuria (T)
b) Massive proteinuria (F)
c) Anasarca (F)
d) Local edema (T)
e) Hypoglycaemia (F)

Q. Renal tumours are- (RMU-22M)
a) Wilm's tumour (T)
b) Renal fibroma (F)
c) Renal edema (F)
d) Renal cell carcinoma (T)
e) Renal failure (F)

Q. Features of nephrotic syndrome includes- (DU-21Ja,20Nv/M,18Ja)
a) Massive proteinuria (T)
b) RBC cast in urine (F)
c) Hypercholesterolemia (T)
d) Massive hematuria (F)
e) Lipiduria (T)

Q. Diagnostic tests for renal disorders are- (CU-19Nv)
a) Serum creatinine (T)
b) BUN (T)
c) Serum androgens (F)
d) AC-125 (F)
e) Renal biopsy (T)

Q. Followings are associated with AGN (RU-19M)
a) Proliferation of mesangial cells (T)
b) Massive proteinuria (F)
c) Thickening of basement membrane (F)
d) RBC cast in urine (T)
e) Classical pathway of complement activation (T)

Q. Features of nephrotic syndrome (DU-18M)
a) Haematuria (F)
b) Massive proteinuria (T)
c) Generalized edema (T)
d) Hypertension (F)
e) Hyperlipidaemia (T)

Q. Cause of urinary tract obstruction are- (RU-18M)
a) Urinary calculi (T)
b) Carcinoma of prostate (T)
c) Uterine prolapse (T)
d) Adenomyosis (F)
e) Pregnancy (T)

Q. Causes of nephrotic syndrome include (DU-17Nv)
a) Post streptococcal glomerulo-nephritis (T)
b) Minimal change disease (T)
c) Diabetic nephropathy (F)
d) Rapidly progressive glomerulo-nephritis (T)
e) Lupus nephritis (T)

Q. Primary glomerulopathies are: (RU-17M)
a) Rapidly progressive glomerulonephritis (T)
b) Amyloidosis (F)

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c) IgA nephropathy (T)
d) Goodpasture syndrome (F)
e) Alport syndrome (F)

Q. Renal cell carcinoma: (DU-16Ja,15Ju)
a) has association with VHI gene (F)
b) many present with painless haematuria (T)
c) can arise from adrenal gland (F)
d) occurs in children (F)
e) can cause polycythemia (T)

Q. Urinary findings of nephrotic syndrome include: (DU-15Ju)
a) Hyaline cast (T)
b) RBC cast (F)
c) Pyuria (F)
d) Proteinuria above 3.5 gm/day (T)
e) Lipiduria (T)

Q. The nephrotic syndrome is accompanied by - (DU-13Ju)
a) decreased glomerular capillary permeability (F)
b) oedema (T)
c) hypertension (F)
d) hypolipidaemia (F)
e) non-selective proteinuria (T)

Q. Urinary findings of nephrotic syndrome include - (DU-11Ja)
a) Hyaline cast (T)
b) Plenty of pus cells (F)
c) Plenty of RBC (F)
d) RBC cast (F)
e) Oxalate crystals (F)

Q. Common causes of obstructive uropathy include - (DU-10Ja)
a) Nodular hyperplasia of prostate (T)
b) Renal infarcts (F)
c) Urinary calculi (T)
d) Normal pregnancy (T)
e) Sickle cell disease (F)

Male Genital System

Q. Biomarkers for diagnosis of testicular tumors are- (CMU-22M)
a) Alpha-feto protein (T)
b) HCG (T)
c) LDH (F)
d) CEA (F)
e) CA-125 (F)

Q. Nodular hyperplasia of prostate- (CMU-22M)
a) Results from stimulation by DHT (T)
b) Typically peripheral zone is involved (T)
c) Hyperplasia of glandular and stromal component (T)
d) TURP is the golden standard treatment (T)
e) Frequent malignant transformation occurs (F)

Q. Germ cell tumours of testis are (DU-19M)
a) Seminoma (T)
b) NHL (F)
c) Choriocarcinoma (T)
d) Teratoma (T)
e) Yolk sac tumour (T)

Q. Nodular hyperplasia of prostate characterized by (RU-19M)
a) Common in men older than age 50 years (T)
b) Considered to be a premalignant lesion (F)
c) After leads to urinary obstruction (T)
d) Occurs in peripheral zone of prostate (F)
e) Microscopically reveals proliferation of both stromal and epithelial cells (T)

Q. Carcinoma prostate is associated with (DU-18Ja)
a) Production of hormone (F)
b) Raised acid phosphatase level (T)
c) Hypercalcemia (F)
d) Frequent bony metastasis (T)
e) Raised PSA level (T)

Q. Seminoma is: (RU-17M)
a) Most common testicular tumour in young (T)
b) Seminoma cells are large and distinct cell membrane (T)
c) The cells produces AFP and HCG (F)
d) It is a sex cord stromal tumour (F)
e) Poor prognosis (F)

Q. Carcinoma of prostate: (DU-16Ja)
a) is a hormone dependent tumour (T)
b) has a soft feeling during P/R examination (F)
c) is related to raised acid phosphatase (T)
d) is associated with hypercalcemia (F)
e) metastasis causes osteosclerosis (T)

Q. Serum PSA level is raised in: (DU-15Ja)
a) Acute prostatitis (T)
b) Nodular hyperplasia (F)
c) Testicular neoplasm (F)
d) Carcinoma of seminal vesicle (F)

MCQ of Systemic Pathology

e) Adenocarcinoma of prostate (T)

Q. Nodular hyperplasia of prostate: (DU-14Ju)
a) is related to dehydrotestosterone stimulation (T)
b) occurs in elderly male (T)
c) typically involves the peripheral region of prostate (F)
d) show proliferation of both glands and stroma (T)
e) is risk factor of prostate carcinoma (F)

Q. Seminoma - (DU-13Ju)
a) is a testicular tumour of infant (F)
b) usually presents with advanced clinical stage (F)
c) has better prognosis than other germ cell tumour (T)
d) is radio-resistant (F)
e) has uniform population of large cells (T)

Q. Carcinoma of prostate - (DU-14Ja)
a) Is a hormone dependent tumour (T)
b) Has soft feeling in PR examination (F)
c) Shows osteosclerotic lesion (T)
d) Show high PSA (T)
e) May have normal acid phosphatase level (F)

Q. Prostatic carcinoma - (DU-12/09Ja)
a) Is usually a squamous cell carcinoma (F)
b) Metastasize to lumbosacral spine (T)
c) Produce osteolytic bony lesion (F)
d) Shows regression with oestrogen therapy (T)
e) Secrets alkaline phosphatase (F)

Q. Nodular hyperplasia of prostate - (DU-10Ju)
a) Is related to dihydrotestosterone stimulus (T)
b) Occurs in about 90% male over 70 years of age (F)
c) Typically involves the peripheral region of prostate (F)
d) Is histologically composed of both gland and stroma (T)
e) Is a risk factor for prostatic adenocarcinoma (T)

Female Genital System

Q. Following tumours are germ cell origin of ovary: (DU-23Nv)
a) Granulosa cell tumour (F)
b) Choricarcinoma (F)
c) Clear cell carcinoma (F)
d) Brenner tumour (F)
e) Yolk sac tumour (T)

Q. Hormone producing tumours of ovary: (DU-22M)
a) Clear cell carcinoma (F)
b) Granulosa cell tumour (T)
c) Dysgerminoma (F)
d) Fibroma (F)
e) Brenner tumour (F)

Q. Gestational trophoblastic disease are: (RMU-22M)
a) Hydrocele (F)
b) Hydatidiform mole (T)
c) Invasive mole (T)
d) Leiomyosarcoma (F)
e) Embryonal carcinoma (F)

Q. Dysfunctional uterine bleeding occurs in: (RMU-22M)
a) Precocious puberty (F)
b) Anovulatory cycle (T)
c) Abortion (F)
d) Inadequate luteal phase (T)
e) Ectopic pregnancy (F)

Q. Hormone producing tumours of ovary: (DU-21Ja,20Nv/M,17M)
a) Dysgerminoma (F)
b) Leydig cell tumor (T)
c) Granulosa cell tumor (T)
d) Teratoma (F)
e) Serous cystadenoma (F)

Q. Risk factors for carcinoma cervix include: (RU-19M)
a) HPV infection (T)
b) Late menarche (F)
c) Genital infection caused by *E. coli* (F)
d) Early age of first intercourse (T)
e) Oral contraceptives (T)

Q. Germ cell tumours of ovary are: (DU-18M)
a) Brenner tumour (F)
b) Dermoid cyst (T)
c) Yolk sac tumour (T)
d) Granulosa cell tumor (F)
e) Thecoma (F)

Q. Dysfunctional uterine bleeding occur in: (RU-18M).
a) Chronic cervicitis (F)

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b) Anovulatory cycle (T)
c) Salpingitis (F)
d) Inadequate luteal phase (T)
e) Ectopic pregnancy (F)

Q. Complications of endometriosis are: (RU-17M)
a) Infertility (T)
b) Urinary frequency (F)
c) Severe dysmenorrhoea (T)
d) Abortion (F)
e) Ectopic pregnancy (F)

Q. Following are sex cord stromal tumors of ovary: (DU-17Ja)
a) dysgerminoma (F)
b) granulosa cell tumor (T)
c) arrhenoblastoma (F)
d) choriocarcinoma (F)
e) yolk sac tumor (F)

Q. Ovarian tumour may be associated with: (DU-16Ju)
a) Pleural effusion (T)
b) Raised CA-125 (T)
c) Hyponatraemia (F)
d) Raised α-fetoprotein (T)
e) Raised CA-15-3 (F)

Q. Germ cell tumors of ovary include: (DU-15Ja)
a) brenner tumor (F)
b) teratoma (T)
c) dysgerminoma (T)
d) granulose cell tumor (F)
e) yolk sac tumor (T)

Q. Endometrial carcinoma is associated with: (DU-15Ja)
a) HPV infection (T)
b) OCP (T)
c) Nulliparity (F)
d) Diabetes mellitus (F)
e) Hypertension (F)

Q. Ovarian tumour may be associated with the following features - (DU-14Ja)
a) Raised PSA (F)
b) Ascitis (F)
c) Pleural effusion (T)
d) Raised CA-125 (T)
e) Hypercalcemia (T)

Q. Most common sites of endometriosis are - (RU-14Ja)
a) Ovaries (T)
b) Fallopian tube (T)
c) Urinary bladder (F)
d) At sites of laparotomy (T)
e) Vermiform appendix (T)

Q. Following are related with endometrial carcinoma - (RU-13Ju)
a) Anovulatory cycle (T)
b) Medullary carcinoma breast (F)
c) Papillary carcinoma thyroid (F)
d) HRT (Hormone Replacement Therapy) (T)
e) Progesterone secreting tumour, ovary (T)

Q. The following are germ cell tumour of ovary - (DU-13Ja)
a) Teratoma (T)
b) Brener tumour (F)
c) Dysgerminoma (T)
d) Choriocarcinoma (F)
e) Sertoli Leydig cell tumour (F)

Q. Uterine leiomyoma - (DU-13Ja,12Ju)
a) Are the most common gynaecological tumour (T)
b) Often causes menorrhagia if submucous type (T)
c) Require progesterone for growth (F)
d) Usually regresses during pregnancy (F)
e) Are the precursor of uterine leiomyosarcoma (T)

Q. Positive pregnancy test is observed in - (DU-12Ja)
a) amenorrhoea (F)
b) hydatidiform mole (T)
c) choriocarcinoma (T)
d) endometrial hyperplasia (F)
e) dysgerminoma (F)

Q. Precancerous lesion of female genital tract include - (DU-12Ja)
a) CIN-II (T)
b) endometrial polyp (F)
c) condyloma accuminatum of the vulva (T)
d) endometriosis (F)
e) atypical hyperplasia of endometrium (T)

Q. Germ cell tumours of ovary include - (DU-10Ja)
a) Teratoma (T)
b) Androblastoma (F)
c) Yolk sac tumour (T)
d) Dysgerminoma (T)

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d) CA-19-9 (T)
e) Nuliparity (F)

Q. Following factors are considered in the etiology of breast cancer - (DU-12Ju)
a) genetic factors (T)
b) atypical ductal hyperplasia (T)
c) smoking habit (T)
d) chronic breast abscess (F)
e) hypertension (F)

Q. Risk factors of breast cancer include - (DU-12Ja)
a) close relatives with breast cancer (T)
b) early menarche (T)
c) early menopause (F)
d) endometrial carcinoma (T)
e) progesterone therapy (F)

Q. Major prognostic factors in breast cancer - (DU-11/10Ju)
a) Invasion (T)
b) Metastasis (T)
c) Oestrogen receptors (F)
d) Histologic subtypes (T)
e) Inflammatory carcinoma (F)

Q. Risk factors for breast cancer include - (DU-08Ju)
a) Close relative with breast cancer (T)
b) Early menarche (T)
c) Early menopause (F)
d) Endometrial carcinoma (F)
e) Increased progesterone (F)

Endocrine System

Q. Microscopic features of nodular goiter are- (CMU-22M)
a) Encapsulation of nodules (T)
b) Varying sizes of follicles (T)
c) Granulomatous inflammation (F)
d) Areas of haemorrhage & calcification (F)
e) Formation of lymphoid follicles (F)

Q. Graves' disease is associated with: (DU-21Oct/M)
a) High T_3 & T_4 level (T)
b) High TSH (F)
c) Hyperplasia of thyroid (T)
d) Dermopathy (T)
e) Bradycardia (F)

Q. Insulin dependent (Type 1) diabetes mellitus is characterized by- (DU-21Ja,20Nv/M,18Ja)
a) Early onset (T)
b) Patients are commonly obese (F)
c) Associated with significant genetic factor (F)
d) Autoimmune destruction of islet cell (T)
e) Hypoglycemic coma is frequent (T)

Q. Papillary carcinoma of thyroid is associated with: (DU-19Nv)
a) Worse prognosis (F)
b) Common among thyroid malignancy (T)
c) Rapid metastasis (F)
d) Psammoma body (T)
e) Characteristic nuclear feature (T)

Q. Features of papillary thyroid carcinoma are: (DU-19M)
a) Presence of psammoma body (T)
b) Ground glass nuclei (T)
c) Arises from parafollicular cells (F)
d) Worse prognosis (F)
e) Increased serum calcitonin (F)

Q. Graves' disease is associated with: (DU-18M)
a) High T_3 & T_4 level (T)
b) High TSH (F)
c) Focal hyperplasia of thyroid (F)
d) Dermopathy (T)
e) Exopthalmous (T)

Q. Graves' disease is characterized by: (DU-16Ju)
a) Pre-tibial myxoedema (T)
b) Hyperplasia of thyroid acini (T)
c) Decreased T_3 & T_4 (F)
d) Raised TSH (F)
e) Presence of thyroid autoantibody (T)

Q. Hyperthyroidism occurs in: (DU-16Ja)
a) lymphocytic thyroiditis (F)
b) Hashimoto's thyroiditis (F)
c) toxic adenoma (T)
d) iodine deficiency (F)
e) Graves' disease (T)

Q. Following are neoplasm of thyroid - (DU-12Ju)
a) medullary carcinoma (T)
b) papillary carcinoma (T)
c) squamous cell carcinoma (F)
d) hurthle cell adenoma (F)
e) anaplastic carcinoma (T)

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e) Brenner tumour (F)

Q. Precancerous lesions of female genital tract include - (DU-08Ju)
a) CIN-II (T)
b) Endometrial polyp (T)
c) Condyloma accuminatum of the vulva (T)
d) Endometriosis (F)
e) Atypical hyperplasia of endometrium (T)

The Breast

Q. Risk factors for breast cancer: (DU-22Nv)
a) Early menarche (T)
b) Early menopause (F)
c) Hormone replacement therapy (T)
d) Family history (T)
e) Increase progesterone (F)

Q. Risk factors for breast cancer include: (BUP-22Nv)
a) Increasing age (T)
b) Infertility (T)
c) Oestrogen therapy (T)
d) Breast feeding (F)
e) Obesity (T)

Q. Prognostic factors of breast carcinoma- (CMU-22M)
a) Invasion (F)
b) Metastasis (T)
c) Estrogen and progesterone (T)
d) Atypical hyperplasia (F)
e) Inflammatory carcinoma (F)

Q. Breast lumps are associated with: (RMU-22M)
a) Pain (T)
b) Nipple discharge (T)
c) Fibrocystic change (T)
d) Peau de orange appearance (T)
e) Krukenberg tumours (T)

Q. Risk factors for breast carcinoma are: (CU-19Nv)
a) Germline mutations (T)
b) First degree relatives with breast cancer (T)
c) Obesity (T)
d) Breast feeding (F)
e) Severe exercise (F)

Q. Risk factors for breast cancer include: (DU-19M)
a) Increasing age (T)
b) Infertility (F)
c) Estrogen therapy (T)
d) Breast feeding (F)
e) Obesity in young women (F)

Q. Fibrocystic changes of breast include: (RU-19M)
a) Adenosis (T)
b) Dysplasia of ductal epithelial cells (F)
c) Epithelial hypoplasia (F)
d) Apocrine metaplasia (F)
e) Herthle cell changes (F)

Q. Risk factors for carcinoma of breast are: (RU-18M)
a) Old age (T)
b) Late menopause (T)
c) Family history (T)
d) Fibrocystic change of breast (F)
e) Fibroadenoma (F)

Q. Risk factors for breast cancer are: (DU-16Ju)
a) Increased mammographic density (T)
b) Early age at 1st live birth (T)
c) Young obese women (F)
d) Breast feeding (F)
e) Postmenopausal HRT (T)

Q. The following bears good prognosis for breast cancer: (DU-15Ja)
a) Positive BRCA-1 & BRCA-2 gene (F)
b) Positive ER & PR gene (T)
c) Well differentiation (T)
d) In situ comedocarcinoma (T)
e) High proliferative rate (F)

Q. Risk factors of breast cancer include - (DU-13Ja)
a) Close relative with breast cancer (T)
b) Early menarche (T)
c) Early menopause (F)
d) Endometrial carcinoma (F)
e) Increased progesterone (F)

Q. Followings are associated with duct cell carcinoma of breast - (RU-13Ja)
a) Hematogenous metastasis (F)
b) Oestrogen (T)
c) Hemorrhage in tumour mass (F)

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Q. Primary causes of hypothyroidism include - (DU-08Ju)
a) Thyroid dysgenesis (T)
b) Pituitary failure (F)
c) Iodine deficiency (T)
d) Hashimoto's thyroiditis (T)
e) Hypothalamic failure (F)

Q. Characteristics of type-I DM include - (DU-08Ju)
a) Markedly decreased blood insulin (T)
b) 100% concordance in twins (F)
c) Linkage to MHC class-II HLA genes (T)
d) Late insulitis (F)
e) No anti-islet cell antibodies (F)

The Skin

Q. Disorders of skin due to melanocytes defect- (CMU-22M)
a) Vitiligo (T)
b) Melasma (T)
c) Nevus (T)
d) Psoriasis (F)
e) Acne vulgaris (F)

Q. Benign adnexal tumors of the skin are: (CU-19Nv)
a) Keratoacanthoma (T)
b) Trichoepithelioma (F)
c) Benign fibrous histiocytoma (F)
d) Cvlindroma (T)
e) Sebaceous adenoma (T)

Q. Pre-malignant lesions of skin include- (RU-17M)
a) Paget's disease (F)
b) Psoriasis (F)
c) Keratoacanthoma (F)
d) Basal cell carcinoma (F)
e) Leukoplakia (T)

Q. Pre-malignant lesions of skin are- (RU-17M)
a) Seborrheic keratosis (F)
b) Actinic keratosis (T)
c) Leukoplakia (T)
d) Nevus (F)
e) Marjollin's ulcer (F)

Bones, Joints & Soft Tissue

Q. Characteristics of pyogenic osteomyelitis: (DU-23Nv)
a) Always occur by blood borne infection (F)
b) May be induced by viruses (T)
c) Commonest organism is *E. coli* (F)
d) Sequestrum formation (F)
e) Chronicity is a common consequence (T)

Q. Ewing sarcoma is characterized by: (DU-22M)
a) Involvement of long bone only (F)
b) Metaphysis is commonly affected (F)
c) Affected area shows onion skin appearance radiologically (T)
d) Painful presentation is common (T)
e) Prognosis is always favourable (F)

Q. Malignant tumours of bone are- (DU-21Oct/M,19M)
a) Paget's disease (F)
b) Osteoblastoma (F)
c) Multiple myeloma (T)
d) Ewing's tumour (T)
e) Chordoma (T)

Q. Osteosarcoma- (CU-19Nv)
a) is a secondary malignant tumor of bone (F)
b) is a malignant tumor that produce cartilage (F)
c) Majority occurs in younger men (T)
d) Presented as painful gradually enlarging mass (T)
e) Majority occurs around the wrist joint (F)

Q. Osteomyelitis related to- (RU-18M)
a) Pathological fracture (T)
b) Sequestrum formation (T)
c) No new bone formation (F)
d) Salmonella typhi may cause it (T)
e) Only bone is inflammed (F)

Q. Pyogenic osteomyelitis- (DU-17M)
a) Occurs by blood born infection (T)
b) is caused by bacteria (T)
c) is caused frequently by streptococcus (F)
d) frequently shows granuloma (F)
e) frequently reveals new bone formation (T)

Q. Pyogenic osteomyelitis- (DU-17Ja)
a) always occurs by blood born infection (F)
b) is caused usually by bacteria (T)
c) is caused commonly by streptococcus (F)
d) frequently shows granuloma (F)

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e) frequently forms new bone (T)

Q. Bone forming tumour include - (DU-16Ju)
a) Giant cell tumour (F)
b) Osteoid osteoma (T)
c) Enchondroma (F)
d) Chondroblastoma (F)
e) Osteosarcoma (T)

Q. Ewing's sarcoma - (DU-11Ju)
a) is a childhood tumour (T)
b) occurs in epiphysis of long bone (F)
c) is associated with p53 gene mutation (F)
d) has prominent necrosis (T)
e) has characteristic lytic lesion in X-ray (T)

Q. Osteomalacia - (DU-09Ja)
a) May occur in coeliac disease (T)
b) Is associated with normal serum alkaline phosphatase level (F)
c) Is characterized by excessive osteoid formation which is poorly mineralized (T)
d) May be complicated by treatment with phenobarbitone (T)
e) Is associated with atrophy of parathyroid gland (F)

Nervous System

Q. Glioma includes: (DU-23M)
a) Astrocytoma (T)
b) Oligodendroglioma (T)
c) Schwannoma (F)
d) Neurofibroma (F)
e) Ependymoma (T)

Q. Following tumours are glioma - (DU-11Ju)
a) meningioma (F)
b) medulloblastoma (F)
c) astrocytoma (T)
d) craniopharyngioma (F)
e) oligodendroglioma (T)

Q. Tumours of glial cells include - (DU-09Ja)
a) Astrocytoma (T)
b) Meningioma (F)
c) Ependymoma (T)
d) Medulloblastoma (F)
e) Oligodendroglyoma (T)

UNIT 04

CLINICAL PATHOLOGY

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CHAPTER 01

LIVER FUNCTION TEST AND JAUNDICE

Liver Function Tests

Q. Enumerate the functions of liver.
Ans.

Functions of liver:

- **Secretory function:** Formation and secretion of bile.
- **Metabolic function (Nutrient & vitamin metabolism):** Liver is the main organ for almost all types of metabolism of glucose and other sugars, amino acids, lipids (fatty acids, cholesterol, lipoproteins), fat-soluble vitamins & water-soluble vitamins. It is the main site for alcohol metabolism.
- **Synthetic function:** Synthesis of plasma proteins (*except* gamma globulins), vitamin-K dependent clotting factors- (II, VII, IX, X), steroid binding and other hormone-binding proteins.
- **Excretory function:** It excretes drug, alcohol, bilirubin, hormone, cholesterol etc.
- **Storage function:** Liver stores glycogen, vitamin- A, D, B_{12}, iron, folic acid etc.
- **Detoxification function:** Liver detoxifies/ inactivates toxin, steroids, other hormones, NH_3 & drugs such as penicillin, ampicillin, erythromycin etc.
- **Haemopoietic function:** In first trimester of fetus, liver is the main site of production of red blood cells.

(Ref: Guyton/11th/860-862; Davidson's/21st/923-925)

Q. What do you mean by liver function test? (DU-09Ja)
Q. Enumerate the different liver function tests. (DU-23M, SMU-23M,22Nv/M, RMU-23M)
Q. What are the common liver function tests? Give their normal value. (DU-22M,18/17Ja,13Ju, 11/09Ja, RU-14Ja,10Ju, CU-11Ju)
Q. Enumerate the important liver function tests. (DU-13Ja, RMU-22M,18M/Ja,17M,14/12Ju, SUST-21Nv,20Nv,19M,16Ja,13Ju,11Ja, CU-20M,16Ju,15Ja)
Q. Enumerate the liver function tests with their clinical significance. (RU-12Ju, SU-11Ja)
Q. Name 5 liver function tests with their normal level. (DU-16Ja, CU-18M)

Q. Write the different liver function tests with their clinical interpretation. (DU-06Ja, RU-15/09Ju)
Q. Mention the indications / significance of liver function tests. (RU-14Ju, SU-09Ju)
Q. What are the tests you will suggest to know the synthetic activity of liver? (RU-17/13Ja,11Ju)
Q. Short note: Liver function tests (LFTs). (DU-19M,18Nv,06M, RU-16/08Ju) ***(V.V.I for VIVA)***
Ans.
Liver function tests: The liver function tests (LFTs) are the *biochemical investigations* to assess the capacity of the liver to carry out any of the function it performs.

The major liver function tests are-

1. **Tests for excretory function:**
   a. **In blood-**
      - ***Serum bilirubin*** concentration (Normal ***0.3-1 mg/dl*** or ***5-17 µmol/L***)
      - Conjugated and unconjugated bilirubin *(in serum, bilirubin is normally almost all unconjugated)*
   b. **In urine-** Urinary bilirubin, urobilinogen
   c. **In stool-** Stercobilinogen

2. **Tests for enzymatic function:**
   a. **Evidence of hepatocellular damage *(as in hepatitis)*:**
      - Alanine aminotransferase (ALT/ SGPT) [10 - 40 U/L]
      - Aspertate aminotransferase (AST/ SGOT) [10 - 35 U/L]
   b. **Evidence of biliary obstruction *(as in obstructive jaundice)*:**
      - Alkaline phosphatase (ALP) [40 - 125 U/L]
      - γ-glutamyl transferase (GGT) [*Male:* 10 - 55 U/L, *Female:* 5 - 35 U/L]

3. **Tests for synthetic function:**
   a. Serum albumin level (Normal 4.8 gm/dl) {*Range:* 3.5 - 5.0 gm/dl} *(A falling serum albumin indicates severity of* chronic liver disease *& thus it is a* bad prognostic sign*)*
   b. Albumin / globulin ratio (Normal 1.7 : 1)
   c. Prothrombin time (Normal 12-16 sec) *{It is a sensitive indicator of both* acute *and* chronic *liver disease)*
   d. Serum total protein concentration (Normal 6 - 8 gm/dl)

4. **Tests for detoxification function:** Serum ammonia concentration.

5. **Other biochemical tests:**
   a. Serum electrolytes (*Hyponatraemia* may occur in *sever liver disease*)
   b. Blood urea level
   c. Serum iron, transferring saturation, serum ferritin level *(Hereditary haemochromatosis)*
   d. Serum & urinary copper *(Wilson's disease)*
   e. Serum ceruloplasmin *(Wilson's disease)*

6. **Tumour marker:** α-fetoprotein (AFP) for *hepatocellular carcinoma.*

7. **Viral markers:** Different viral markers for different types of viral hepatitis (A, B, C, D & E).

8. **Immunological tests:** For autoimmune liver diseases-
   a. Anti-mitochondrial antibody *(Primary biliary cirrhosis)*
   b. Antinuclear antibody *(Autoimmune hepatitis)*
   c. Anti-smooth muscle antibody *(Autoimmune hepatitis).*

(Ref: Lecture SSMC & DMC; Prof. Khaleque/196)

Indication / significance of liver function tests:
1. Differential diagnosis and progress of jaundice
2. To assess the extent of liver damage
3. To follow the progress of liver damage

4. To identify the specific cause of liver damage
5. To investigate possible complications.

(Ref: Davidson's/20th/940; Prof. Khaleque/196; Lecture SSMC & DMC)

Q. What are the enzymes are elevated in hepatocellular and obstructive jaundice? (DU-21Oct/M)

Ans.

Enzymes elevated in hepatocellular jaundice:

1. Alanine aminotransferase (ALT/ SGPT)
2. Aspertate aminotransferase (AST/ SGOT)

Enzymes elevated in obstructive jaundice:

1. Alkaline phosphatase (ALP)
2. γ-glutamyl transferase (GGT).

Q. Name the common liver function tests. (DU-15Ja)

Q. Mention 4 important liver function tests. (CU-12Ju)

Ans.

Common liver function tests: ***(V.V.I for VIVA)***

- Serum bilirubin
- ALT & AST
- Alkaline phosphatase (ALP)
- Prothrombin time (PT)
- Serum total protein and albumin
- Albumin / globulin ratio.

Q. What are the expected changes of liver function tests in chronic liver diseases and acute viral hepatitis? (DU-11Ja)

Q. What alteration will occur in liver function test in acute viral hepatitis? (DU-17M)

Ans.

Expected changes of liver function tests in chronic liver diseases and acute viral hepatitis:

In chronic liver diseases:

- Plasma albumin: *Low*
- Albumin : Globulin ratio: *Altered*
- Prothrombin time (PT): *Prolonged*
- Alkaline phosphatase: *Markedly raised*
- γ-glutamyl transferase: *Raised*
- Serum bilirubin: *Raised*
- AST & AST: *Raised*

In acute viral hepatitis:

- Serum bilirubin: *High*
- ALT & AST: *Very high*
- Alkaline phosphatase: *Slightly high*
- Viral markers: *Positive.*

Q. A male of 40 years had a history of jaundice six months back. Now he has developed distension of abdomen with gynaecomastia and haemorrhoid. What is the likely diagnosis? Name the liver function tests that are expected to be altered. (DU-12Ju)

Ans.

Likely diagnosis: Chronic liver disease (CLD).

Expected changes in liver function tests in CLD: *Please see above.*

Q. Enumerate the laboratory tests / investigations for diagnosis of liver disease.

Ans.

Investigations for diagnosis of liver disease:

A. Liver function tests:
- Serum bilirubin
- Serum aminotransferases (ALT & AST)
- Gamma-glutamyl transferase (GGT)
- Alkaline phosphatase (ALP)
- Prothrombin time (PT)
- Serum total protein and albumin
- Albumin / globulin ratio
- Urinary bilirubin and urobilinogen
- Complete blood count (CBC)
- Specific aetiological investigations, e.g.
  - Viral markers in hepatitis A, B, C, D and E
  - α-fetoprotein (AFP) in hepatocellular carcinoma
  - Immunological tests (auto antibodies) for autoimmune liver disease (e.g. *primary biliary cirrhosis)*
  - Serum iron, transferring saturation, serum ferritin in *hereditary haemochromatosis*
  - Serum & urinary copper, and serum ceruloplasmin in *Wilson's disease*

B. Imaging of liver (CT scan or MRI)

C. Liver biopsy.

(Ref: Davidson's/20th/940; Prof. Khaleque/196; Lecture SSMC & DMC)

Exclusive Questions for VIVA from Liver Function Test

Q. Name four diseases or conditions where liver function tests are done.

Ans.

Four diseases or conditions where liver function tests are done:
1. Coagulation disorders
2. Obstructive jaundice
3. Liver cirrhosis
4. Hepatocellular carcinoma.

Q. Write down the importance of prothrombin time. (DU-18Ja)

Q. Name two causes of raised prothrombin time. (DU-22M,17Ja)

Q. Short note: Prothrombin time. (CU-20Ju)

Ans.

Importance of prothrombin time: Prothrombin time (PT) is a coagulation screening test that measures how long it takes blood to clot. It is the ***most sensitive & most specific*** indicator of both acute and chronic liver disease.

Causes of raised prothrombin time:
- Deficiency of factor I, II, V, VII, X (১০ তলায় ১২৫৭)
- Liver disease
- DIC
- Vitamin K deficiency
- Warfarin therapy.

{***N.B:*** A PT test may also be called an INR (international normalized ratio) test which stands for a way of standardizing the results of prothrombin time tests}

Q. Why prothrombin time is more specific than total protein estimation? (DU-09Ja) ***(Must be asked in VIVA)***

Ans.

Prothrombin time is more specific than total protein estimation: Prothrombin is produced ***only*** by ***liver***. Whereas, some plasma proteins such as ***immunoglobulins*** are produced outside the liver (i.e. by ***plasma cells***). So, total protein concentration in blood does not directly reflect the status of liver function. That's why ***prothrombin time*** is ***more specific than total protein*** estimation.

Q. Which one is more liver specific ALT/AST and why?

Ans.

ALT is ***more specific*** for liver damage ***than AST***, as AST is also present in heart, brain, kidney and muscle. High levels of AST are seen in hepatic necrosis as well as myocardial infarction, congestive cardiac failure and muscle injury.

Q. Which are the best markers of CLD (chronic liver disease)?

Ans.

Best markers of CLD (chronic liver disease):

a. Total protein and albumin/globulin ratio
b. Prothrombin time (PT).

(***N.B:*** Always remember, PT is better than total protein).

Q. Mention the sites where ALP is found.

Ans.

Sites where ALP (alkaline phosphatase) is found:

a. Liver (bile duct)
b. Bone
c. Intestine
d. Placenta.

Q. In which situation ALP may be increased?

Ans.

Situation where ALP may be increased:

a. Cholestatic jaundice (4-6 times than normal limit)
b. Bone disease
c. Pregnancy.

Q. How will you differentiate whether increased ALP is due to cholestasis or not? ***(For Honors gainers)***

Ans.

If **cholestasis** → Both ALP & GGT is increased.

If **other than cholestasis** (i.e. bone disease or pregnancy) → Only ALP is increased.

Q. What are the markers of alcoholic liver disease?

Ans.

Markers of alcoholic liver disease:

a. GGT
b. AST.

Remember:
- ALT → Viral hepatitis
- AST → MI + Non-viral hepatitis
- ALP → Cholestasis + Bone disease + Pregnancy
- GGT → Alcoholic liver disease + Cholestasis.

Q. Which type of anaemia may be found in CLD?
Ans.
Type of anaemia may be found in CLD: Usually macrocytic.

Hyperbilirubinemia

Normal bilirubin concentration in blood
- ***Total bilirubin:*** 0.3 - 1 mg/dl (5 - 17 µmol/L)
- ***Direct (conjugated) bilirubin*** = 0.25 mg % (6 µmol/L)
- ***Indirect (unconjugated) bilirubin*** = 0.75 mg % (11 µmol/L)

Hyperbilirubinemia stands for serum bilirubin > 1 mg % (1 mg/dl).

Q. What do you mean by direct and indirect bilirubin?
Q. What is indirect bilirubin? (CU-20/10Ju)
Ans.
Direct bilirubin: Conjugated bilirubin is called ***direct bilirubin***. In aqueous solution, it is water soluble, and reacts rapidly (within one minute) with the reagent diazotized sulfanilic acid in **van den Bergh** reaction. That's why it is called "direct reacting" or direct bilirubin.

Indirect bilirubin: Unconjugated bilirubin is called ***indirect bilirubin***. It is ***not soluble in water***. In plasma, it is bound to the albumin. It is obtained by subtracting the 'direct reacting' bilirubin from the total bilirubin.
(Ref: Lippincott's/3rd/283; Prof. Khaleque/194)

Q. State the causes of unconjugated hyperbilirubinemia. (CU-16Ja)
Q. Short note: Unconjugated hyperbilirubinemia. (DU-12Ja)
Ans.
Unconjugated hyperbilirubinemia: It is a clinical condition in which there is increased level of ***unconjugated bilirubin*** in blood.

Cause:
- Excess production of bilirubin *(e.g. haemolytic anaemia)*
- Reduced hepatic uptake *(e.g. Gilbert's syndrome)*
- Impaired bilirubin conjugation *(e.g. physiological jaundice of the newborn)*.

Clinical importance: Fraction of unconjugated bilirubin (very small amount) may remain unbound and diffuse into the tissues particularly in the brain of infants and produce toxic injury (***kernicterus***).
(Ref: Lecture SSMC; Prof. Khaleque/194)

Q. State the differences between conjugated & unconjugated bilirubin. (SU-16Ja)
Q. State the differences between direct & indirect bilirubin. (CMU-22M)
Q. Short note: Unconjugated bilirubin. (CU-09Ja)
Ans.
Differences between conjugated and unconjugated bilirubin: ***(For Honors gainers)***

Traits	Unconjugated bilirubin	Conjugated bilirubin
1. Presence / absence in healthy person	Present in blood in healthy person	Absent in blood in healthy person
2. Solubility	Water insoluble	Water soluble
3. Passage in urine	It can not pass in urine	It can pass in urine (bilirubinuria)
4. CNS damage	Lipid soluble & thus can cause damage to CNS (particularly in the brain of infants and produce toxic injury – *kernicterus*)	Relatively lipid insoluble & cause no damage to CNS
5. Binding	Tightly bound with plasma albumin	Weakly associated with albumin
6. van den Bergh reaction	Indirect positive (indirect reacting bilirubin)	Direct or immediate positive (direct reacting bilirubin)
7. Increased in	Haemolytic jaundice	Hepatocellular & obstructive jaundice

(Ref: Lecture SSMC & DMC; Prof. Khaleque/194,195)

Nice to Know:

Congenital non-hemolytic hyperbilirubinaemia: *(For Honors gainers)*

Syndrome	Pattern of inheritance	Defect of bilirubin metabolism	Type of hyperbilirubinaemia
Gilbert's syndrome	Autosomal dominant	Low hepatic uptake of unconjugated bilirubin	Unconjugated
Crigler-Najjar syndrome-I	Autosomal recessive	Absence of glucuronyl transferase enzyme	Unconjugated
Crigler-Najjar syndrome-II	Autosomal dominant	Deficiency of glucuronyl transferase enzyme	Unconjugated
Dubin-Johnson syndrome	Autosomal recessive	Decreased hepatic excretion of conjugated bilirubin	Conjugated
Rotor syndrome	Autosomal dominant	Decreased hepatic excretion of conjugated bilirubin	Conjugated

Jaundice

Q. Define (DU-23M,17Nv,16Ja,08Ju, SU-20M,15Ju;14Ja,12/11Ju, RU-18Nv,17Ju/Ja,16/13/10Ja, CU-15/08Ja) **and classify jaundice.** (DU-23M,05Ja, SU-20M,14Ja,11Ju, RU-18Nv,17Ju,16/15/13/10Ja, CU-15/08Ja)

Q. What are the causes of jaundice? (SU-20M)

Q. What are the clinicopathological types of jaundice? Give example. (SU-10Ju)

Q. Mention important causes of obstructive jaundice. (CMU-22Nv, RU-18Ja)

Ans.

Jaundice: Jaundice may be defined as a clinical condition characterized by yellow discoloration of the skin, sclera and mucous membranes due to an increased bilirubin concentration in the body fluid above normal.

Normal serum bilirubin: 0.3 - 1 mg/dl (5 - 17 µmol/L)

Clinical jaundice: When bilirubin in plasma exceeds **3 mg/dl** (50 µmol/L).

Latent jaundice: Clinically, there is no jaundice but serum bilirubin is **more than normal** but **less than 3 mg/dl**.

Classification of jaundice with causes:

A) ***Pathophysiological classification*:**

1. **Predominantly unconjugated hyperbilirubinaemia:**
   - Excess production of bilirubin *(e.g. haemolytic anaemia)*
   - Reduced hepatic uptake *(e.g. Gilbert's syndrome)*
   - Impaired bilirubin conjugation *(e.g. physiological jaundice of the newborn).*
2. **Predominantly conjugated hyperbilirubinaemia:** Intrahepatic & extrahepatic cholestasis.

B) ***Clinico-pathological classification*:**

1. **Haemolytic / pre-hepatic jaundice:** It results from excessive breakdown of RBC & excessive production of ***unconjugated bilirubin***.

   Causes:
   - Congenital defect in RBC e.g. sickle cell anaemia, thalassaemia, haemoglobinopathies
   - Incompatible blood transfusion
   - Malaria
   - *Pyruvate kinase* deficiency
   - *Glucose 6- phosphate dehydrogenase* deficiency
   - Autoimmune hemolytic disease
   - Certain drugs e.g. quinine
   - Snake venom
   - Erythroblastosis foetalis
2. **Hepatocellular / hepatic jaundice:** Damage to the liver cells can cause ***unconjugated bilirubin*** level to increase in the blood as a result of decreased conjugation.

   Causes:
   - Viral hepatitis
   - Chronic alcoholic hepatitis
   - Liver cirrhosis
   - Infections e.g. Yellow fever, septicaemia
   - Poisons e.g. arsenic, CCl_4, phosphorus etc.
   - Paracetamol poisoning
   - Cardiac failure
3. **Obstructive / post-hepatic jaundice:** This is due to an obstruction of the bile duct that prevents the passage of bile into the intestine. This condition is called ***cholestasis*** (i.e. the failure of bile secretion). The obstruction may be ***intrahepatic*** or ***extrahepatic***. The bilirubin in the serum is ***conjugated***.

   Causes: *(None will pass without saying this at VIVA)*

   i) **Intra-hepatic cholestasis:** This is due to parenchymal liver damage, or excretory dysfunction of *bile canaliculi* at a cellular level.
      - Viral hepatitis
      - Drugs *(e.g. methyltestosterone, estrogen, oral contraceptives)*
      - Primary biliary cirrhosis
      - Alcoholic hepatitis
      - Pregnancy
      - Post-operative.

   ii) **Extra-hepatic cholestasis:** Obstruction in the biliary tract distal to *bile canaliculi*.
      - Stone in common bile duct
      - Carcinoma of head of the pancreas or ampulla of vatter
      - Metastatic carcinoma of common bile duct
      - Stricture of common bile duct
      - Cysts in common bile duct

- Ascaris impaction in common bile duct
- Pressure from outside by enlarged coeliac lymph nodes
- Traumatic biliary stricture.

(Ref: Lecture SSMC & DMC; Prof. Khaleque/194,195)

Q. What is choluric jaundice?

Q. What is acholuric jaundice? (DU-10Ja) ***(Frequently asked in VIVA)***

Ans.

Choluric jaundice: Jaundice with ***presence of bilirubin in urine*** is called choluric jaundice. So, hepatitis and obstruction of the common bile duct (obstructive jaundice) causes choluric jaundice.

Acholuric jaundice: Jaundice ***without presence of bilirubin in urine*** is called acholuric jaundice. Hemolytic jaundice is acholuric type.

(Ref: Prof. Khaleque/195)

Q. Give the laboratory findings of different types of jaundice. (DU-08Ju, SMU-23M,22Nv/M,20Nv,19M, RU-15Ju)
Q. Give the biochemical findings of different types of jaundice. (DU-22Nv)
Q. How different types of jaundice can be diagnosed in the laboratory? (RU-17Ja)
Q. Mention the differences between different types of jaundice. (DU-17Nv, RU-18Nv,17Ju,16Ja)
Q. Differentiate different types of jaundice biochemically. (DU-10Ja)
Q. How you will differentiate different type of jaundice in the laboratory? (DU-06S, SU-20M, RU-13/11/10Ja)
Q. Mention the laboratory differences of haemolytic and hepatocellular jaundice. (SU-11Ja, CU-08Ja)
Q. Give the differences between haemolytic and obstructive jaundice. (DU-15/14Ja)
Q. How will you differentiate obstructive jaundice from hepatocellular jaundice in the laboratory? (DU-07Ju, BUP-22M, SUST-21Nv,14Ja,11Ju, CU-16/12Ju,05Ja)
Q. How will you investigate hepatocellular jaundice? (SU-09Ju)
Q. How obstructive jaundice can be investigated in the laboratory? (SU-18M,13Ju,12Ja,10Ju, 06Ja)
Q. What abnormalities in LFT are expected in a case of obstructive jaundice? (CU-15Ju)
Q. Write down the urinary and stool findings of obstructive jaundice. (RU-15Ja)
Q. Give the urinary findings of a case of obstructive jaundice. (DU-21Oct/M,16Ja)
Q. Differentiate clinicopathological types of jaundice by urine examination. (RU-09Ju)
Q. How urine examination helps in differential diagnosis of different types of jaundice? (RU-12Ja)
Q. What are the biochemical changes in hepatic jaundice? (CU-19M)

Ans.

Laboratory findings of jaundice/ important tests to differentiate different types of jaundice:

A. Blood biochemistry:

Test	Hemolytic jaundice	Hepatocellular (hepatic) jaundice	Obstructive jaundice
Serum bilirubin	Raised (mostly **unconjugated**)	Raised (both **conjugated** and **unconjugated**)	Raised (**conjugated**)
Alkaline phosphatase (ALP)	Normal	Small rise	**Very high**
AST / SGOT	Normal	**Markedly raised**	Slightly raised
ALT / SGPT	Normal	**Markedly raised**	Slightly raised
Prothrombin time (PT)	Normal	Prolonged	Prolonged
Serum albumin	Normal	Low	Normal

B. Haematological tests:

Test	Hemolytic jaundice	Hepatocellular jaundice	Obstructive jaundice
Haematological test	Findings of haemolytic anaemia	Leucopenia in viral hepatitis	No significant findings

C. Urine:

Test	Hemolytic jaundice	Hepatocellular jaundice	Obstructive jaundice
Bilirubin	Absent	Variable	**Present**
Urobilinogen	Increased	Normal or increased	Decreased
Bile salts	Absent	Absent	Present
Van den Berg reaction	Indirect positive	Direct positive	Direct positive

D. Stool:

Test	Hemolytic jaundice	Hepatocellular jaundice	Obstructive jaundice
Naked eye	Dark *(due to excess bile pigment)*	Normal color or pale	**Pale** or **normal colour. Bulky, frothy** due to **high fat content**
Stercobilinogen	Increased	Reduced	Reduced
Fecal fat	Absent	Increased	Increased

E. Special blood test:

Test	Hemolytic jaundice	Hepatocellular jaundice	Obstructive jaundice
Viral markers (HBsAg, HBeAg etc.)	Not found	Found in viral hepatitis	Not found
α-fetoprotein	Not found	Found in hepatocellular carcinoma	Not found

(Ref: Samson Wright's/13/46; Prof. Khaleque/195; Lecture SSMC & DMC)

(Please read the above chart at least 10 times for passing VIVA exam.)

Q. Give the interpretation of raised serum bilirubin.

Ans.

Interpretation of raised serum bilirubin:

	Hemolytic jaundice	Hepatocellular jaundice	Obstructive jaundice
Serum bilirubin	Markedly raised *(mostly unconjugated)*	Raised *(both conjugated and unconjugated)*	Raised *(conjugated)*

Q. Write down the interpretations of ALT, AST and alkaline phosphatase in different types of jaundice? (DU-13Ja)

Ans.

Interpretations of ALT, AST and alkaline phosphatase in different types of jaundice:

Enzyme	Hemolytic jaundice	Hepatocellular jaundice	Obstructive jaundice
ALT / SGPT	Normal	Markedly raised	Slightly raised
AST / SGOT	Normal	Markedly raised	Slightly raised
Alkaline phosphatase (ALP)	Normal	Small rise	Very high

Obstructive / Post-Hepatic Jaundice

Q. Give the etiology & pathogenesis of obstructive jaundice.

Q. Mention the causes of obstructive jaundice. (DU-07Ju, CMU-22Nv)
Q. Short note: Obstructive jaundice. (DU-13Ju, SU-19Nv)
Ans.
Obstructive / post-hepatic jaundice:

Etiology / Causes: *Please write from above.*

Pathogenesis:

Intrahepatic & extrahepatic bile flow obstruction
↓
Bile cannot drains into the intestine
↓
Absorption of bile in blood (containing conjugated bilirubin)
↓
Conjugated hyperbilirubinaemia
↓
Obstructive jaundice.

Liver function test in obstructive jaundice;

1. **Serum bilirubin:** *Conjugated hyperbilirubinaemia.*
2. **Serum alkaline phosphatase level:** *Markedly raised.*
3. **Prothrombin time:** *Prolonged.*
4. **Urinary urobilinogen:** *Reduced or absent.*
5. **Stool stercobilinogen:** *Reduced or absent.*

Complications of obstructive jaundice: ***(Very Important for VIVA)***

1. Deposition of bile salt in the skin - ***pruritus.***
2. Absence of bile salts in the gut - ***indigestion and malabsorption (steatorrhoea).***
3. Presence of bilirubin in the urine - ***dark urine.***

Q. Why prothrombin time is prolonged in obstructive jaundice? (BUP-22M)
Ans.
Prothrombin time is prolonged in obstructive jaundice: Obstruction of the bile duct and intrahepatic cholestasis result in vitamin-K deficiency due to impaired lipid absorption → Impairment in the synthesis of vitamin-K dependent clotting factors (II, VII, IX, X) → Prolonged prothrombin time (PT).

Q. A 30 years old female presented with jaundice, pruritus, bulky pale stool with raised alkaline phosphatase. What is your clinical diagnosis? Write down the extra-hepatic causes of the lesion. (DU-22M)
Ans.
Clinical diagnosis: Obstructive jaundice.

Extra-hepatic causes of obstructive jaundice: *Please see above.*

Q. A male of 60 years old presented with severe jaundice with history of carcinoma of head of the pancreas. What type of jaundice it is? What will be the findings of LFT and urine of this patient? (BUP-22Nv,21Nv/M,20Nv/M)
Ans.
Type of jaundice: Obstructive jaundice.

Findings of LFT and urine in a patient with obstructive jaundice: *Please see above.*

Q. A known case of haemolytic anaemia presents with jaundice with itching all over the body. Ultrasonography shows gall stone. What type of jaundice is this? What are the expected changes in liver function test? (DU-15Ju)

Ans.

Type of jaundice: Obstructive jaundice.

Changes in the liver function test: *Please see above.*

Q. A female of 45 years having multiple stone in gall bladder developed jaundice with itching. Examination revealed palpable gall bladder. What type of jaundice is this? What changes do you expect in the liver function test? (DU-14Ju)

Ans.

Type of jaundice: Obstructive jaundice.

Changes in the liver function test: *Please see above.*

Physiological Jaundice

Q. What is physiological jaundice? (DU-14Ja, RU-17Ja)

Q. Short note: Physiological jaundice.

Ans.

Physiological (normal) jaundice: Most infants develop visible jaundice due to elevation of **unconjugated bilirubin** concentration during their **first week**. This common condition is called **physiological jaundice**. It generally **appears at 2-4 days of age** and **disappears by 1 to 2 weeks of age**. It is **harmless** and doesn't usually cause a problem.

This mild jaundice is due to the immaturity of the baby's liver, which leads to a slow processing of bilirubin.

Mechanism / reasons: Normally, bilirubin passes through the liver and is excreted as bile through the intestines. Jaundice occurs when bilirubin builds up faster than a newborn's liver can break it down and pass it from the body. Reasons for this include-

1. Newborns make more bilirubin than adults do since they have more turnover of red blood cells
2. A newborn baby's still-developing liver may not yet be able to remove adequate bilirubin from the blood
3. Too large an amount of bilirubin is reabsorbed from the intestines before the baby gets rid of it in the stool.

Treatment: Treatment is usually not needed. For most babies, jaundice usually gets better **without treatment within 1 to 2 weeks**. Sometimes **phototherapy** is needed for infants **whose bilirubin levels are very high**.

Possible complications: Rare, but serious, complications from high bilirubin levels include:

- Cerebral palsy
- Deafness
- Kernicterus *(brain damage from very high bilirubin levels)*.

Q. Why jaundice appears in premature baby? (RU-15Ja)

Ans.

Causes of jaundice in premature baby: In premature baby liver can not properly conjugate bilirubin. As a result, jaundice occurs due to ***unconjugated hyperbilirubinaemia***. They develop jaundice on or after 2nd or 3rd day of life and resolves by **14 days**. The baby is otherwise healthy.

The peak level of ***unconjugated hyperbilirubinaemia*** may be 10-12 mg/dl on the 5th day of life and may rise to maximum **15 mg/dl**, and then falls, the direct fraction is <15% of the total.

Q. Short note: Kernicterus. (DU-11Ju)

Ans.

Kernicterus: Kernicterus is a neurological syndrome resulting from bilirubin toxicity within the brain – staining and necrosis of neurons in the basal ganglia, hippocampal cortex, subthalamic nuclei & cerebellum followed by gliosis of those areas. The cerebral cortex is usually spared.

Etiology / causes:

1. Prematurity
2. Hemolytic disease of the newborn
3. Congenital familial non-hemolytic jaundice
4. Neonatal hepatitis
5. Congenital spherocytosis.

Treatment:

1. Appearance of clinical signs suggesting bilirubin toxicity or encephalopathy is an indication for exchange transfusion at any level of serum bilirubin
2. Once established, kernicterus is irreversible and management is only symptomatic.

(Ref: M R Khan/3rd/69,70)

Exclusive Questions for VIVA from Jaundice

Q. Mention 3 cardinal features of obstructive jaundice. ***(For Honors Gainers)***

Ans.

3 cardinal features of obstructive jaundice:

1. Conjugated bilirubin
2. Generalized itching
3. Pale stool and urinary bilirubin is present.

Q. Why there is generalized itching in obstructive jaundice? ***(For Honors Gainers)***

Ans.

Cause of generalized itching in obstructive jaundice: Due to cholestasis, bile salt can not excreted; accumulation occurs in skin & causes degranulation of mast cell, results in increased release of histamine resulting in generalized itching.

Q. Why there is pale stool in obstructive jaundice? ***(For Honors Gainers)***

Ans.

Cause of pale stool in obstructive jaundice: No bile → No digestion of fat → Steatorrhoea & ultimately pale stool.

Q. Why bilirubin is present in urine? ***(For Honors Gainers)***

Ans.

Causes of presence of bilirubin in nurine:

- **In obstructive jaundice:** Conjugated bilirubin → Water soluble → So, can be excreted through urine.
- **In haemolytic jaundice:** Unconjugated bilirubin → Not water soluble → Not excreted through urine.

CHAPTER 02

RENAL FUNCTION TEST

Renal Function Tests

Q. What are the renal function tests? (DU-15Ju,14Ja,12Ju/Ja,10/09Ju, BUP-22M, RU-17M,13Ju/Ja,12/11Ja, CU-13Ju,07Ja, SU-15Ju,10Ja) **Give their normal levels and units of measurements.** (DU-22Nv,14Ja)
Q. Name the important renal function tests. (DU-22Nv,16Ju, CU-20Ju,16Ja)
Q. Name the 5 important renal function tests. (CU-11Ja)
Q. What are the special tests in urine examination? (RU-11Ja)
Q. What are the chemical tests done in urine examination? (DU-13Ju/Ja, SU-20Nv,19M,11Ja)
Q. Mention the laboratory interpretation of urine analysis. (RU-10Ja)
Q. Write the findings to be noted in routine analysis of urine. (CU-20Nv)
Q. Mention the organic and inorganic substances found in urine. (CU-15Ja)
Q. How will you diagnose the renal disorders in the laboratory? (CU-20M)
Q. Short note: Renal function tests. (DU-22M, SU-20Nv, RU-19/18M,16Ju)

Ans.

Renal function tests: Renal function tests are common laboratory tests used to evaluate the function of kidneys. These are as follows:

1. **Routine examination of urine:**

Examination	Normal urinary findings
A. Physical examination:	
Quantity	800 - 2,500 ml /day (minimum 650 ml)
Colour	Straw
Odour	Pungent
Appearance	Clear
Sedimentation	Nil
Specific gravity	1.010 - 1.020

B. Chemical examination:	
Reaction (pH) - Litmus paper test	Acidic (4.8 - 8)
Albumin - Heat coagulation test	Trace (< 200 mg /day)
Sugar - Benedict test	Nil
Excess phosphate	Nil
On request-	
Bile salts - Hay's surface tension test	Absent
Bile pigment (bilirubin) - Fouchet' test	Absent
Ketone bodies - Rothera's test	Absent
Urobilinogen	Absent
Bence-Jones protein	Absent
C. Microscopic examination:	
Cells-	
RBC	Absent
Pus cells	0- 3 / HPF (in male), 0- 5 / HPF (in female)
Epithelial cell	Occasional
Casts-	
RBC casts	Absent
WBC casts	Absent
Epithelial casts	Absent
Granular casts	Absent
Hyaline casts	Absent
Crystals and others-	
Urates	Absent
Uric acid	Absent
Calcium oxalate	Absent
Amorphus phosphate	Absent
Triple phosphate	Absent

2. **<u>Blood analysis</u>:**
   - Blood urea (15 - 40 mg /dl ***or,*** 2.5-6.6 µmol/L)
   - Serum creatinine (0.7 - 1.4 mg /dl ***or,*** 60-120 µmol/L) ***(No. 1 test in kidney function)***
   - Serum electrolytes (Na^+: 134-145 mmol/L, K^+: 3.6-5.1 mmol/L, Cl^-: 95-107 mmol/L etc.)
3. **<u>Renal clearance tests</u>:**
   - Creatinine clearance test (70 - 140 ml/min)
   - Urea clearance test (60 - 70 ml/min)
   - Inulin clearance test (125 ml/min)
4. **<u>Imaging tests</u>:**
   - Plain X-ray KUB region
   - Ultrasonography (USG)
   - Intravenous urography (IVU)
   - CT scan
   - MRI
   - Retrograde pyelography & cystoscopy
   - Renal arteriography & venography
5. **<u>Radionuclide study</u>:** Renography.
6. **Renal biopsy.**

(Ref: Lecture SSMC; Davidson's/22nd/466-471)

Q. Write down the significance of renal function test. (RU-13Ju)

Q. Describe briefly the importance of urine examination.
Q. Enumerate the indications of routine urine examination. (RU-14Ja)
Q. Enumerate the importance of routine urine examination. (RU-12Ja)
Q. Enumerate the diseases that can be diagnosed by urine examination. (RU-17Nv,15Ju,08Ja)
Ans.

Importance of urine examination:

1. Diagnosis of renal disease and assessment of their severity, e.g.
   - Urinary tract infection (UTI)
   - Nephrotic syndrome
   - Acute glomerulonephritis (AGN)
   - Neoplasms in urinary tract
   - Lesions of prostate and seminal vesicle (in male)
   - Calculi (stone) in urinary tract
2. Assessment of the prognosis of renal disease
3. Investigation of the cause of
   - Edema and proteinuria
   - Electrolyte imbalance
   - Acid-base disorders
4. Monitoring of the treatment of renal disease
5. Diagnosis of metabolic and systemic diseases, e.g.
   - Diabetes mellitus
   - Diabetes insipidus
   - Jaundice
6. Diagnosis of pregnancy.

(Ref: Lecture SSMC, DMC)

Q. Write briefly about urine examination. (RU-18Ja)
Ans.
Urine examination: *Please write from above 2 (two) questions (routine examination of urine + importance of urine examination).*

Q. Illustrate the importance of physical test of urine. (For VIVA
Ans.
Clinical importance of physical examination of urine:

a. **Volume:** May be polyuria, oligouria, anuria.
   - ***Polyuria*** (> 3000 ml/day) found in:
     1. Diabetes mellitus
     2. Diabetes insipidus
   - ***Oliguria*** (< 400 ml /day) found in:
     1. Renal failure and cardiac failure
     2. Excessive loss of fluid in diarrhea, vomiting or burn
     3. Acute glomerulonephritis (AGN)
     4. Nephrotic syndrome
     5. Urinary tract obstruction
   - ***Anuria*** (< 50 ml/day) found in:
     1. Shock
     2. Bilateral obstruction of ureters.

b. Colour:

- ***Straw colour:*** Normal urine due to urochrome and urobilinogen
- ***Yellow:*** In jaundice (due to bilirubin or excess urobilinogen)
- ***Red:*** Due to Hb and RBC
- ***Milky:*** Due to chyluria
- ***Pinkish / orange:*** Due to rifampicin (anti-TB drug)

c. Appearance:

- ***Cloudy*** in presence of RBC, WBC, epithelial cells, excessive pus cell
- ***Turbid*** in urinary tract infection

d. Specific gravity and osmolarity:

- ***Increase in:***
  1. DM and cardiac failure
  2. Dehydration & SIADH
- ***Decrease in:***
  1. Diabetes insipidus
  2. Acute renal failure.

(Ref: Lecture SSMC, DMC)

Nice to Know: *(V.V.I for VIVA)*

Few common definitions:

Anuria: It is defined as failure to pass urine more than 50 mL in 24 hours

Oliguria: Failure to pass more than 400 mL of urine in 24 hours

Nocturia: Need to get up during the night to pass urine

Polyuria: Passing of large volume of urine more than 3 L in 24 hours

Frequency of micturition: Repeated scanty urination.

(Ref: Long Cases in Clinical Medicine/1st/378)

Q. Mention the different abnormal colours of urine. (RU-13/11Ju)

Q. Short note: Colour of urine in different conditions. (RU-15Ju)

Ans.

Abnormal colours of urine:

Abnormal colours of urine	Associated condition
1. Colourless	Diluted urine due to- ▪ Much drinking ▪ Nervousness ▪ Diabetes incipidus ▪ Diabetes mellitus
2. Deep straw	Highly concentrated urine
3. Greenish yellow to deep straw to darkish	▪ Eating certain vegetables ▪ Drugs ▪ Vitamins ▪ Bilirubin ▪ Haemoglobin ▪ Methaemoglobin ▪ Melamine ▪ Homogentisic acid
4. Whitish yellowish	▪ Pyoria
5. Smoky	▪ Microscopic hematuria
6. Reddish to red	▪ Hematuria

	▪ Certain drugs *(e.g. rifampicin, clofazimine, phenindione, purgative like phenolphthaline etc.)*
7. Milky	▪ Chyluria

Nice to Know:

Causes of black urine: Fresh urine is normal, but when kept for hours, it turns dark-

- Acute intermittent porphyria
- Alkaptonuria.

(Ref: Long Cases in Clinical Medicine/1st/378)

Q. Give the clinical importance of chemical examination of urine. *(For VIVA)*

Ans.

Clinical importance of chemical examination of urine:

1. **pH:** Low (acidic) in normal condition and acidosis.
2. **Albumin** - Heat coagulation test *(found positive in proteinuria)*
3. **Sugar** - Benedict test *(found positive in DM)*
4. **Bile salts**- Hay's sulfur test *(found positive in obstructive jaundice)*
5. **Bile pigment (bilirubin)** - Fouchet's test *(found positive in conjugated hyperbilirubinemia)*
6. **Ketone bodies** - Rothera's test *(found positive in ketosis and ketoacidosis)*
7. **Blood** - Orthotolidin test *(found positive in hematuria, hemoglobinuria).*

(Ref: Lecture SSMC, DMC)

Nice to Know:

In urine- Plenty of pus cells indicate UTI.

(Ref: Lecture SSMC)

Q. Short note: Urinary crystals. (RU-18Ja, CU-12Ju)

Ans.

Urinary crystals: Crystalluria indicates that the urine is supersaturated with the compounds that comprise the crystals, e.g. ammonium, magnesium and phosphate for struvite.

1. **Common crystals**
   - Calcium oxalate dihydrate
   - Struvite / triple phosphate
   - Bilirubin
   - Calcium carbonate
   - Amorphous
2. **Pathological crystals**
   - Calcium oxalate monohydrate
   - Ammonium biurate
   - Cholesterol
   - Cystine
   - Leucine
   - Tyrosine
3. **Crystals due to drugs** (e.g. sulfadiazine).

Factors influencing urinary crystal formation:

1. Lifestyle
2. Diet

3. Dehydration (leading to concentrated urine formation)
4. Changes in urinary pH
5. Inability of the chemicals to neutralize the process of crystal formation
6. Urinary tract infections
7. Kidney infections
8. Metabolic disorders.

(Ref: Geoffrey K. Dube and Robert S. Brown)

Q. What do you mean by casts in urine? (CU-19Nv) **Enumerate casts in urine.** (RU-11Ja)
Q. What are the organized deposits of urine? (CU-14Ja)
Q. Mention the different types of casts found in urine and give its importance. (RU-15Ja)
Q. Write four important casts in urine with corresponding diseases. (SU-14Ju)
Q. Short note: Casts in urine / Urinary casts. (CMU-22M,12/11Ja,10Ju, RU-20M,17Ju,16Ja, 12Ju,10Ja)
Q. Short note: Casts in urine with interpretation. (RU-13Ju)
Ans.
Casts: These are ***solidified*** or ***coagulated proteins*** formed in the renal tubules. These are microscopic narrow cylindrical structures with parallel sides and rounded ends, varying in size and shape. Common casts are ***cellular casts*** (epithelial, RBC, and WBC), ***granular cast*** and ***hyaline cast***.

1. **Epithelial casts-** Found in renal tubular necrosis (RTN)
2. **RBC casts-** Found in acute glomerulonephritis (it is the **hallmark of AGN**)
3. **WBC casts-** Found in pyelonephritis
4. **Granular casts-** Found in glomerulonephritis
5. **Hyaline casts-** Normal findings.

(Ref: Prof. Khaleque/203; Long Cases in Clinical Medicine/1st/376; Lecture SSMC)

Q. Write the microscopic findings of urine in pathological conditions. (SU-14Ju)
Q. Enumerate the diseases that can be diagnosed by urine examination. Explain with clinical and laboratory findings. (RU-15Ju)
Ans.
Microscopic findings of urine in pathological conditions:

1. **RBC:** Different causes of ***haematuria***, such as-
   - Acute glomerulonephritis (AGN)
   - Acute pyelonephritis
   - Renal calculi
   - Renal tuberculosis
   - Renal cell carcinoma
   - Neoplasm of ureter, urinary bladder and urethra
   - Bleeding disorders e.g. haemophilia, thrombocytopenia, DIC
   - Overdose of anticoagulant therapy
   - Inflammation: e.g. cystitis, urethritis etc.
   - Trauma to any part of urinary tract
2. **Pus cells:** Urinary tract infection.
3. **Epithelial cells:** Increased epithelial cell signifies contaminated urine, that is not appropriate for culture.
4. **Different casts:**
   - **Epithelial casts-** Found in renal tubular necrosis (RTN)
   - **RBC casts-** Found in acute glomerulonephritis (AGN)
   - **WBC casts-** Found in pyelonephritis

- **Granular casts**- Found in glomerulonephritis
- **Hyaline casts**- Normal findings.

5. **Different crystals** (e.g. Calcium oxalate, struvite / triple phosphate): Different types of renal, ureteric or urinary bladder stones.

Q. Mention the indications of renal biopsy.

Ans.

Indications of renal biopsy:

1. Unexplained acute renal failure
2. CKD (chronic renal failure) with normal sized kidney
3. Nephrotic syndrome in adults
4. Steroid non-responsive nephrotic syndrome in children
5. Isolated haematuria or haematuria.

(Ref: Davidson's/21st/469; Lecture SSMC)

Q. State the procedure for collection of sample of urine for routine examination. (CU-10Ju)

Ans.

Procedure for collection of sample of urine for routine examination:

- Urine is collected in a clean, dry, sterile pot / sterilized test tube
- For male: Mid-stream urine is normally collected
- For female:
  - Before collection, vulva and vestibule must be washed with soap and ringed with dry cloth
  - She must urinate keeping vulva apart
  - Mid-stream urine is collected
- After collection of urine sample, it should be labeled properly and then submitted for examination
- Fresh urine is to be examined within a few hours *(unorganized deposits may appear if left at room temperature. There is also chance of bacterial contamination).*

(Ref: Prof. Khaleque/201)

Q. What do you mean by renal clearance test? (DU-07Ju, RU-13Ju,12Ja)

Q. State the importance of renal clearance test.

Q. Short note: Renal clearance test.

Ans.

Renal clearance test: It is the virtual volume of plasma **(in ml)** that is completely cleared of a particular substance by both kidneys in **each minute.**

Or,

Renal clearance may be defined as the virtual volume of plasma which contains the amount of that substance excreted through urine per minute.

$$\text{Renal clearance (ml/ min)} = \frac{\text{Concentration of substance in urine} \times \text{volume of urine (ml/min)}}{\text{Concentration of substance in plasma (in ml)}}$$

Examples:

Renal clearance of inulin (C_{inulin}) = 125 ml/ min
Renal clearance of creatinine ($C_{creatinine}$) = 70-140 ml/ min
Renal clearance of urea (C_{urea}) = 60-70 ml/ min

Importance of plasma clearance:

1. It is a good marker of renal function.
2. Assessment of severity of renal impairment.
3. Measurement of GFR, RPF and RBF.
4. Calculation of filtration fraction.

5. Monitoring of drug.
6. It can be used to quantify the basic functions of kidney-glomerular filtration, tubular reabsorption and tubular secretion.

Uremia & Azotemia

Q. What do you mean by uremia & azotemia? (RU-18Nv,17Nv/Ju,16Ja,14Ju,13/11Ju,07Ja, SU-14/12Ja,09Ju,06/05Ja, CMU-23M,11Ju,08/07Ja)
Q. What is azotemia? (RMU-21Nv, CU-17M,16Ja)
Q. Mention the causes of uremia. (DU-15/03Ja, SU-09Ju, CU-07Ja)
Q. Mention the pre-renal causes of uremia. (RU-14Ju)
Q. Mention the causes of high urea level in blood. (SU-14Ja, CU-03Ja)
Q. Short note: Azotemia. (CU-14Ja)
Q. Short note: Uremia. (CMU-22Nv, SU-13/10Ju)
Ans.
Azotemia: Azotemia is a **biochemical abnormality** indicating an increase of **blood urea nitrogen (BUN)** & **creatinine** level.

(Ref: Prof. Khaleque/197)

Uremia: Presence of excessive amount of creatinine, urea and other nitrogenous waste products in the blood is called uremia.

(Ref: Lecture SSMC)

Or,

When **azotemia** becomes associated with clinical **signs & symptoms** and **biochemical abnormalities,** it is termed as **uremia.**

(Ref: Robbins/10th/896)

Or,

Uremia is the **clinical condition** due to an increase of **blood urea nitrogen (BUN)** & **creatinine** level.

(Ref: Prof. Khaleque/197)

Causes of uremia:

1. Pre-renal cause	1. Heart failure 2. Shock 3. Dehydration e.g. severe vomiting, diarrhoea, acute intestinal obstruction 4. Diabetic coma 5. Haemorrhage 6. Loss of blood due to trauma, GIT bleeding, complication of pregnancy 7. Surgical emergency 8. Malaria
2. Renal cause	1. Acute and chronic glomerulonephritis 2. Chronic pyelonephritis 3. Renal tuberculosis 4. Malignant hypertension 5. Mercurial poisoning 6. Systemic lupus erythematosus (SLE)
3. Post-renal cause	1. Prostate enlargement 2. Urethral stricture (e.g. gonococcal urethritis) 3. Carcinoma bladder

(Ref: Lecture SSMC; Prof. Khaleque/197)

Q. Write down the normal levels of blood urea and creatinine. (DU-11Ja)

Ans.

Normal levels of blood urea and creatinine: *(Very Important for VIVA)*

- **Blood urea:** 15 - 40 mg /dl ***or,*** 2.5-6.6 µmol/L
- **Serum creatinine:** 0.7 - 1.4 mg /dl ***or,*** 60-120 µmol/L.

Nice to Know:

Normal value of **BUN** is 7-21 mg/dl.

(Ref: Lecture SSMC)

Q. Write the cause of high blood urea. (SU-14/13/12/06Ja)

Ans.

Causes of high blood urea:

1. Intake of high protein diet
2. Renal failure
3. Gastro-intestinal haemorrhage
4. Trauma
5. Burns
6. Severe infections
7. Use of corticosteroids.

Q. What is the normal serum uric acid level? State the clinical significance of raised serum uric acid level. (DU-03Ja)

Q. Give the clinical importance of serum uric acid. (DU-10Ju,08Ja)

Q. Short note on: Uric acid.

Ans.

Normal plasma level of uric acid: 2 - 7 mg /dl (0.12 - 0.42 mmol /L).

Clinical significance of raised serum uric acid level: Raised serum uric acid level occurs in-

1. Acute glomerulonephritis (AGN)
2. Nephrotic syndrome
3. Acute renal failure
4. Chronic renal failure
5. Urinary tract obstruction
6. Gout
7. Polycythaemia vera
8. Chronic lymphocytic leukaemia (CLL)
9. Lymphoma
10. Eclampsia.

Q. Write the clinical importune of serum creatinine. (DU-11Ju,10Ju/Ja, SU-19Nv,17M)

Q. Short note: Serum creatinine. (CU-15Ja,08Ju)

Ans.

Creatinine: Creatinine is a break-down product of *creatine phosphate* in muscle, and is usually produced at a fairly constant rate by the body (depending on muscle mass).

Normal level: 0.7 - 1.4 mg/dl (60-120 µmol/l).

Causes of increased serum creatinine level:

Reduced excretion in:

1) Renal failure
2) Competition for tubular secretion with some drugs (e.g. trimethoprim, cimetidine)

High production in:

1) Rhabdomyolysis
2) Large muscle mass.

(Ref: Davidson's/20th/461; Lecture SSMC)

Q. Why serum creatinine level is more specific than serum urea level as a renal function test? (DU-14Ja,12Ju, RU-17Ju,16Ja)
Q. Why serum creatinine is more specific renal function test? (DU-09/08Ju, RU-13Ja,10Ju)
Q. Why serum creatinine estimation is more valuable test than estimation of blood urea? (DU-07Ju)
Q. Give the clinical importance of serum creatinine. (DU-11Ju,10Ja)

Ans. ***(Very Important for VIVA)***

Serum creatinine level is more specific than serum urea level as a renal function test: Blood urea is a poor guide to renal excretory function as it ***varies*** with protein intake, liver metabolic capacity and renal perfusion.

Serum creatinine is ***more specific*** as it is produced from muscle at a ***constant rate*** and almost ***completely filtered*** at the glomerulus. If muscle mass remains constant, changes in creatinine concentration reflect changes in GFR.

(Ref: Davidson's/20th/461)

Proteinuria

Q. What is proteinuria? (SMU-23M,22Nv/M, RU-18Ja)
Q. What are the causes of proteinuria? (DU-13Ju, SMU-23M,22Nv/M,21/20Nv,19/18M,15Ju, 12/10Ja, RU-18Ja,16Ju,15/11Ja, CU-15Ja,13/11Ju)
Q. Short note: Proteinuria. (RU-19Nv,18M,17Nv)

Ans.

Proteinuria: Proteinuria means presence of ***protein (mainly albumin) in urine.***

Healthy adult excrete 150-200 mg protein per day, but it cannot be detected by heat coagulation test. A positive heat coagulation test is called ***proteinuria.***

(Ref: Prof. Khaleque/201; Lecture SSMC)

Causes of proteinuria: ***(V.V.I. for VIVA)***

A. Physiological:

1. Postural or orthostatic proteinuria
2. High protein intake
3. Exercise
4. Exposure to cold
5. Following mental strain

B. Pathological:

a. Renal diseases:

1. Nephrotic syndrome *(massive proteinuria)*
2. Nephritic syndrome / AGN
3. Chronic glomerulonephritis *(slight proteinuria)*
4. Pyelonephritis
5. Renal tuberculosis
6. Polycystic kidney disease
7. Diabetic nephropathy *(massive proteinuria)*
8. Toxaemia of pregnancy *(massive proteinuria)*
9. Amyloidosis *(massive proteinuria)*
10. Renal calculi
11. Renal tumours

b. Post-renal diseases:
1. Prostatitis
2. Urethritis
3. Cystitis
4. Calculi of ureter & urinary bladder.

c. Systemic or pre-renal diseases (mild proteinuria)**:**
1. Febrile illness
2. Congestive heart failure
3. Hypertension
4. Hyperthyroidism
5. Systemic disorders associated with haematuria.

(Ref: Prof. Khaleque/201)

Q. What is massive proteinuria? (DU-11Ju,06S, RU-16Ju,15Ja,12Ju,07Ja)
Q. Enumerate the causes of massive proteinuria. (DU-22Nv, RMU-22M,)
Q. What are the diseases that may present with massive proteinuria? (DU-13Ja,11/07Ju, RU-12Ju/Ja,10Ja)
Q. Mention 4 causes of massive proteinuria. (DU-09Ja)
Q. Write short note on: Massive proteinuria. (DU-14/11Ja, RU-17/10Ju)
Ans.
Massive proteinuria: When ***more than 3.5 gm albumin*** passes through urine ***in 24 hours***, it is called massive proteinuria.

Causes of massive proteinuria: ***(110% Important for VIVA)***
1. Nephrotic syndrome
2. Toxaemia of pregnancy
3. Diabetic nephropathy
4. Lupus nephritis
5. Amyloidosis
6. Multiple myeloma.

(Ref: Lecture SSMC & DMC)

Very Important for VIVA:
- **Selective proteinuria:** It means that the urinary protein is mainly albumin and larger molecular weight plasma proteins are present in only small amounts.
- **Highly selective proteinuria:** Larger molecular weight proteins are virtually absent.
- **Non-selective proteinuria:** Larger molecular weight proteins are present in significant amount.

(Ref: Prof. Khaleque/201)

Q. Enumerate the laboratory procedure of detection of protein in urine. (RU-04S/Ja,03Ja)
Q. How can you detect / estimate protein in urine? (RU-18Ja,14Ju,11/08/07Ja)
Q. Name the tests we do for proteinuria. (DU-09Ju)
Q. What are the methods of protein detection in urine? (RU-16Ju, CU-13Ja)
Ans.
Laboratory procedure of detection of protein in urine:

A. Qualitative test (detect just present or not. By this method absolute quantity cannot be measured)
1. Heat coagulation test
2. Reagent strip test (Stix test)

B. Quantitative test (Absolute quantity can be measured)

1. Esbach's albuminometer
2. Sulpho-salicylic acid test.

(Ref: Prof. Khaleque/205)

Q. How do you perform the heat coagulation test of urine? (DU-05/03M)
Q. Write the procedure of heat coagulation test. (SU-12Ja)
Q. Write down the principle of detection of protein in urine. (DU-16Ju)
Q. Write short note on: Heat coagulation test. (RU-17Nv)

Ans.

Boiling test / Heat coagulation test:

Principle: Coagulation of protein is caused by the denaturation of protein structure by heat. (Secondary, tertiary and quarternary structures are loosed, but primary structure remains intact).

Required materials:

- A test tube
- Bunsen burner
- 5% acetic acid
- Supplied urine (or protein solution).

Procedure:

- Abut two-thirds of a test tube is filled with supplied urine
- Then the upper one-third of the solution is heated slowly keeping the test tube at inclined position
- Cloudiness appears which becomes deep on addition of a few drops of 5% acetic acid (glyceal acetic acid). This indicates the presence of albumin
- If cloudiness vanishes on addition of acetic acid, then it is due to excess phosphate present in urine.

Observation of heat coagulation test:

Observation	Inference
Cloudiness:	
Absent	Nil
Distinctly cloudy	+ **(normal)**
Granular appearance	++ **(moderate)**
Granule large, flocculent	+++ **(massive)**

Q. Short note: 24 hours urinary protein. (CU-13Ju)

Ans.

24 hours urinary protein: 24-hour urine protein measures the amount of protein released in urine over a 24-hour period. The test checks the function of the kidneys and detects disease.

Urine samples are collected in one or more containers over a period of 24 hours. The containers are kept in a cool environment and then sent to a lab for analysis. Specialists then check the urine for protein. The test is simple and noninvasive.

When higher than normal amount of protein are in the urine, it is called proteinuria. Proteinuria is often a sign of kidney damage and disease.

Normal value: < 80 mg of protein per day.

Indication:

1. Glomerulonephritis
2. Uncontrolled diabetes
3. High blood pressure
4. SLE
5. Urinary tract infections (UTIs)
6. Multiple myeloma

7. Amyloidosis

Disadvantage:

1. The test does not show what kinds of protein are in the urine.
2. The test also does not show the cause of the protein.
3. Occasionally proteinuria is not a sign of kidney damage (specially for children)
4. Other factors, such as extreme stress, vigorous exercise, dehydration etc. may also influence the test results.

Q. What is microalbumin? Write its importance. (DU-09Ju, RU-12Ja)
Q. Short note: Microalbuminuria? (RU-09Ju)
Ans.

Microalbuminuria: Microalbuminuria describes the urinary excretion of ***small amounts*** of ***normal albumin*** protein ***(30-300 mg/day)*** which is not detected by conventional methods.

Significance of microalbuminuria:

1. Early sign of diabetes nephropathy
2. Increased risk of atherosclerosis and cardiovascular mortality.

(Ref: Davidson's/21st/481; Prof. Khaleque/201)

Nice to Know: *(Very Important for VIVA)*

Postural or orthostatic proteinuria (without organic disease): Protein is detectable in healthy persons in ambulant position, but is absent in the first morning sample or after a period of rest. There is no demonstrable renal disease. The condition is benign.

(Ref: Prof. Khaleque/201)

Q. What do you mean by Bence-Jones protein? (RU-17Nv, CU-14Ju)
Q. How Bence-Jones protein is detected in urine? (SU-10Ja)
Q. Short note: Bence-Jones protein and its detection in urine. (DU-14Ju)
Q. Short note: Bence-Jones protein. (DU-13Ja,10Ju, SU-20/18M,15/09Ja, RU-17Ja,15Ju,13Ja,10Ju, CU-10Ja)
Ans.

Bence-Jones protein: It is an ***immunoglobulin light chain*** either κ (kappa) or λ (lambda).

It is found in various pathological conditions like-

1. Multiple myeloma
2. Macroglobulinaemia
3. Amyloidosis
4. Lymphoma
5. Leukaemia.

(Ref: de Gruchy/5th/306,307)

Detection of Bence-Jones protein in urine:

1. **Heat test:** Bence-Jones proteins have unique behavior in heating. Urine containing Bence-Jones proteins flocculates when heated slowly to 50-60°C. The flocculated proteins on boiling, and reappears on cooling below 60°C.
2. **Electrophoretic method:** The most reliable means for the detection of Bence-Jones proteins is electrophoresis of a concentrated urine specimen on cellulose acetate. The monoclonal light chains usually migrate as a marrow band in the globulin region.

(Ref: de Gruchy/5th/306,307)

Nice to Know:

Significance of quantifying proteinuria: ***(Very Important for VIVA)***

- Normal total protein → Up to 150 mg/day (<30 mg albumin / day)
- Microalbuminuria → 30-300 mg albumin / day
- Tubular proteinuria → <0.5 gm/day
- Glomerular (nephritic range) → <0.5-3 gm/day
- Nephrotic range → >3 gm/day.

Reducing Substances

Q. Classify reducing substance. (CU-15Ju)
Q. What are the reducing agents that can be found in urine? (DU-14/12Ju,05Ja, CMU-21M,09Ja, RU-17Ju)
Q. Short note: Reducing substance in urine. (DU-22Nv, CU-13/12Ja)
Ans.
Reducing substances: Reducing substances are the substances that can reduce Benedict solution.

The most important urinary reducing substances are:

1. **Sugar substances:** Glucose, lactose, pentose, fructose & galactose.
2. **Non-sugar substances:**
   - Homogentisic acid *(present in alkaptonuria)*
   - Nalidixic acid
   - Drugs - Cephalosporin, ascorbic acid or aspirin.

*(**N.B:** Normally **reducing substances** are absent in urine, but in certain conditions they are present in urine. **Glycosuria** is most common. **Lactosuria** occurs in pregnancy and during lactation. **Pentosuria, fructosuria,** and **galactosuria** are rare inborn errors of metabolism.)*

(Ref: Lecture SSMC; Prof. Khaleque/202)

Q. How glucose is detected in urine?
Q. Mention the method of detection of glycosuria. (RU-15Ju)
Q. How do you perform Benedict's test of urine and interpret it? (DU-03S)
Q. How can you detect reducing substance in urine? (RU-17/12Ju)
Q. Write down the principle of detection of reducing substance in urine. (DU-16Ju)
Q. Short note: Benedict's test. (DU-23Nv,21Oct/M)
Ans.

Detection of glucose in urine: ***(V.V.I for Practical Examination)***

A. **Qualitative test:**
   1. **Benedict's test:** Usually done.
   2. **Fehling test:** Obsolete, very costly.
   3. **Reagent strip test:** Specific test for glucose & better for bedside purposes.

B. **Quantitative test:** It can be done by using Benedict's quantitative reagent, but not usually done for practical purpose.

(Ref: Prof. Khaleque/205)

Benedict's test:

Principle: Cupric salt is reduced by glucose in hot alkaline solution to cuprous salt giving a visible color.

Procedure:

1. Take 5 ml of Benedict qualitative reagent in a test tube.
2. Heat the tube over a flame to expel any impurities.

3. Add 8 drops (0.5 ml) of urine & heat again for about 2 min.
4. Then allow cooling.

Observation: The blue color of reagent is changed depending on the presence of amount of reducing substance. Blue → Green → Yellow → Orange → Brick red.

Interpretation:

Observation	Interpretation I inference
Blue (No change)	Reducing substance is absent
Green	+
Yellow	++
Orange	+++
Brick-red	++++

Q. Benedict test only proves that presence of reducing substance in urine. So, how you will be sure that glucose is present in urine?

Ans.

By glucose strip (***Strip tests*** are specific for glucose).

(Ref: Lecture SSMC)

Q. Write the significance of Benedict's test in urine.

Ans.

Significance of Benedict's test in urine: To detect sugar in urine for-

1. Diagnosis of diabetes mellitus
2. Diagnosis of alimentary and renal glycosuria
3. To see prognosis of treatment of diabetes mellitus.

Ketone Bodies in Urine

Q. Name the ketone bodies. (DU-11Ju, RU-14Ju)

Q. Short note: Ketone bodies. (RU-18Nv/Ja,10/08Ju, CU-14Ja, SU-12/05Ja)

Ans.

Ketone bodies: Ketone bodies are reducing substances, formed by the excessive and abnormal fat metabolism.

Ketone bodies are-

1. Acetoacetate
2. β-hydroxybutyrate
3. Acetone

Normal blood & urine ketone bodies:

	In blood	In urine
Ketone bodies	Less than 3 mg/dl or 0.2 mmol/L	Less than 1 mg/day

(Ref: Lippincott's/3rd/195; Harper's/26th/184, 245)

Detection in urine:

1. Rothera's test
2. Acetest (modified Rothera's test)
3. Reagent strip test.

(Ref: Prof. Khaleque/205)

Q. How can you detect ketone bodies in urine? (RU-19Nv,13/11Ju)

Q. Write down the biochemical test for detecting ketone bodies in urine. (RU-17/16Ja,14Ju)

Q. Short note on: Rothera's test. (RU-09Ju)

Ans.

Rothera's test: It is the test of detecting ketone bodies in urine.

Procedure:

1. Saturate a few ml (10 ml) of fresh urine taken in a test tube with ammonium sulphate
2. Add a few granules of powdered sodium nitroprusside
3. Add liquor ammonia forte (2 ml) by the side of the test tube
4. A permanganate (purple) coloured ring at the junction of the two fluids indicates the presence of ketone bodies.

(Ref: Prof. Khaleque/205)

Q. What are the causes of ketonuria? (RU-17/16Ja,11Ju)

Q. Short note: Ketonuria. (DU-16Ju, RU-12Ju)

Ans.

Ketonuria: Acetoacetate, β-hydroxybutyrate, and acetone are collectively called ketone bodies or ketones. Excretion of more than a trace of these substances in the urine is called ***ketonuria***.

(Ref: Lecture SSMC)

Causes of ketonuria:

A. Physiological:
1. Starvation (due to fat breakdown)
2. Diet low in CHO
3. High fat diet

B. Pathological:
1. Uncontrolled DM
2. Severe dehydration following vomiting and diarrhoea
3. Glycogen storage disease.

(Ref: Lecture SSMC)

Q. Define ketonemia and ketosis.

Ans.

Ketonemia: Presence of excess ketone bodies in the blood higher than normal level is called ketonemia.

Ketosis: Ketonemia & ketonuria together is called ketosis.

(Ref: Harper's/28th/191)

Q. How can you detect ketone body, bile salts and chyle in urine? (RU-13Ju)

Ans.

Detection of ketone body, bile salts and chyle in urine:

Substance	Test to detection
Ketone bodies	Rothera's test
Bile salts	Hay's surface tension test
Chyle	Milky white appearance which disappears if fat solvent (e.g. acetic acid) is added. Chylomicron can be visualized under microscope with dark ground illumination or stained with Sudan-III.

Hematuria

Nice to Know:

Blood is present in urine as:
1. **Haematuria-** is the presence of red cells in urine, or
2. **Haemoglobinuria-** haemoglobin passed in urine.

(Ref: Prof. Khaleque/202)

Q. What do you mean by hematuria? (DU-08Ju, SU-20M, RU-17Ju,16Ja,10Ju)
Q. What are the causes of hematuria? (DU-16/13/08Ju, CMU-21Nv/M,20Ju,16Ju/Ja,15Ju/Ja,11Ja,10Ju,09Ja, SU-20M, RU-17Ju/Ja,16Ja,11/10/09Ju)
Q. Write 4 causes of hematuria. (CU-12Ja)
Q. State the renal causes of hematuria. (CU-04Ja)
Q. Short note: Haematuria. (DU-19Nv, SMU-23/22/19M,14Ju,10Ja, CMU-22Nv,11Ju, RU-12Ju)
Ans.
Hematuria: Presence of ***RBC in urine*** is called hematuria. It indicates bleeding from anywhere in the renal tract.

Causes of hematuria: ***(V.V.I for VIVA)***

A. **Renal causes:** Blood is intimately mixed with urine.
1. Acute glomerulonephritis (AGN)
2. Renal calculi
3. Infections – Severe acute pyelonephritis, papillary necrosis, renal tuberculosis
4. Malignant hypertension, infarction, right heart failure
5. Renal cell carcinoma, tumors of renal pelvis
6. Polycystic kidney, solitary cyst
7. Trauma

B. **Post-renal causes:**
1. Trauma to any part of urinary tract
2. Impaction of stone in ureter or urethra
3. Inflammation, e.g. cystitis, urethritis etc.
4. Neoplasm of ureter, urinary bladder and urethra

C. **Pre-renal causes (systemic diseases):** Blood is intimately mixed with urine.
1. Haemorrhagic disorders e.g. haemophilia, thrombocytopenia, DIC
2. Sickle cell anaemia
3. Septicaemia, particularly meningococcal
4. Scurvy
5. Overdose of anticoagulant therapy.

(Ref: Prof. Khaleque/202)

Q. How will you investigate a case of haematuria? (SU-20M)
Ans.
Investigation of a case of haematuria:

1. **Urine:**
   - Microscopic examination of urine for RBC & RBC cast
   - Chemical examination of urine for Hb-
     - Orthotolidine test
     - Benzidine test

2. **Blood (routine):**
   - Hb% - reduced (due to blood loss)
   - ESR - increased
   - BT & CT - may be increased if there is thrombocytopenia or hemophilia
   - WBC count - neutrophilic leukocytosis

3. **Special blood tests:**
   - Serum urea level
   - Serum creatinine level

4. **IVU** (intravenous urogram)
5. **Plane x-ray** of KUB region.

Q. Mention the urinary findings of a case of haematuria?
Ans.

Urinary microscopic findings of a case of haematuria:

1. WBC *(suggestive of infection)*
2. RBC - dysmorphic erythrocytes (phase contrast microscopy) *(suggestive of glomerular bleeding)*
3. RBC casts *(suggestive of glomerular bleeding)*
4. Abnormal epithelial cells *(suggestive of tumour).*

(Ref: Davidson's/21st/479)

Nice to Know:

Haematuria may be-

1. **Gross / macroscopic haematuria:** ***Visible*** and reported by the patient. Appears smoky or red on naked eye examination, and plenty red cells on microscopic examination.
2. **Microscopic haematuria:** ***Invisible*** and detected on dipstick testing of urine. Red cells are only detectable under microscope due to small number.

(Ref: Davidson's/21st/478; Prof. Khaleque/202)

Q. Short note: Microscopic haematuria. (DU-12Ju)
Ans.

Microscopic haematuria: Haematuria which is invisible by naked eye examination, but detectable under microscope *(due to small number)* and on dipstick testing of urine is called **microscopic haematuria.**

Interpretation of dipstick positive haematuria:

- WBC *(suggestive of infection)*
- RBC - dysmorphic erythrocytes (phase contrast microscopy) *(suggestive of glomerular bleeding)*
- RBC casts *(suggestive of glomerular bleeding)*
- Abnormal epithelial cells *(suggestive of tumour).*

Glomerular bleeding characteristically causes **microscopic haematuria**. Whereas **macroscopic (visible) hematuria** is more likely to be caused by tumours and severe infections or renal infarction, usually accompanied by pain.

Management: Management of hematuria depends upon the cause.

(Ref: Davidson's/21st/478,479)

Q. Mention the causes of painless haematuria. (SU-19Nv,17M,13Ju)
Ans.

Causes of painless haematuria:

1. Glomerulonephritis (commonly IgA nephropathy)
2. Renal tuberculosis
3. Tumors of urinary system (renal cell carcinoma, papilloma of the urinary bladder, etc.)
4. Bleeding disorder
5. Anticoagulant or antiplatelet drug therapy
6. Bilharziasis (schistosomiasis)
7. Interstitial nephritis.

(Ref: Long Cases in Clinical Medicine/1st/378)

Q. Write the causes of painful haematuria.
Ans.

Causes of painful haematuria:

1. Renal infection
2. Renal calculi
3. Trauma

4. Polycystic kidney disease (clot colic)
5. Loin pain hematuria syndrome
6. Hemorrhagic cystitis due to cyclophosphamide.

(Ref: Long Cases in Clinical Medicine/1st/378)

Nephrotic Syndrome

Q. Define nephrotic syndrome. (DU-17/16Ja,12Ju, RU-20Nv/M,17/12/10Ja)
Q. Enumerate the causes of nephrotic syndrome. (DU-17M,16Ja,12Ju, RU-18M,16Ju,15/10/08Ja, CU-13Ju)
Q. Enumerate the primary causes of nephrotic syndrome. (SU-08Ja)
Q. Short note: Nephrotic syndrome. (DU-15Ja, RU-14Ja, CU-10Ju,09Ja)
Ans.
Nephrotic syndrome: It is a ***glomerular syndrome*** which is characterized by **massive proteinuria** (≥3.5 gm/day), **hypoalbuminaemia** (plasma albumin level < 3 gm/dl), **generalized edema, hyperlipidaemia** and **lipiduria** (lipid in the urine).

(Ref: Robbins/10th/896,912)

Fig: Patient of nephrotic syndrome.

Causes of nephrotic syndrome: ***(Very Important for VIVA)***

1. **Primary glomerular diseases:**
   - Minimal-change disease (*most common in children*)
   - Membranous glomerulonephritis (*most common in adults*)
   - Membranoproliferative glomerulonephritis
   - Focal segmental glomerulosclerosis
   - IgA nephropathy
2. **Systemic diseases:**
   - Diabetes mellitus
   - Amyloidosis
   - Systemic lupus erythematosus (SLE)
   - Drugs (nonsteroidal anti-inflammatory, penicillamine, heroin)
   - Infections (malaria, syphilis, hepatitis B & C, HIV)
   - Malignancy (carcinoma, lymphoma, myeloma)
   - Miscellaneous (bee sting allergy, hereditary nephritis).

(Ref: Robbins/10th/912; Harsh Mohan/7th/648)

Q. How will you investigate a case of nephrotic syndrome? (DU-04Ja)
Q. Write down laboratory findings in nephrotic syndrome. (RU-17Ju,16Ja)
Q. What urinary findings you expect in nephrotic syndrome? (DU-16Ju,12Ja, SMU-23M,19Nv, CU-12Ju)
Ans.
Laboratory investigations for nephrotic syndrome:

1. **Routine and microscopic examination of urine:**

- **Volume of urine:** Reduced
- **Specific gravity:** Usually raised
- **Albumin:** +++ / ++++ (massive)
- **RBC:** (+ / -)
- **Cast:** Hyaline casts

2. **24 hours urinary total protein estimation:** Usually > 3.5 gm / 24 hrs
3. **Serum albumin:** < 3 gm/dl
4. **Albumin / Globulin ratio:** Reduced
5. **Serum lipid profile:** High cholesterol and high TG may be present
6. **Blood sugar, blood urea, serum creatinine** and **serum electrolytes** should be done
7. **USG of KUB region** to see both kidneys present or not, kidney size, position, any growth
8. **Renal biopsy** (to see the type of glomerular disease, whether minimal, membranous or membranoproliferative) – this will guide for diagnosis, therapy and prognosis.

(Ref: Prof. Khaleque/204; Davidson's/20th/467)

Q. A 7 year old boy presents with massive proteinuria, hypoalbuminemia, generalized edema and hyperlipidemia. Mention your diagnosis and causes of it. (RMU-22M)
Ans.
Diagnosis: Nephrotic syndrome.

Causes of nephrotic syndrome: *Please write from above.*

Nephritic Syndrome / AGN

Q. What do you mean by nephritic syndrome or AGN? (DU-09/08Ja, SU-18M, RU-11Ja)
Q. What are the causes of nephritic syndrome? (RU-19/17M)
Q. How will you diagnose a case of nephritic syndrome? (DU-03Ja)
Q. Write down laboratory findings in nephritic syndrome. (RU-17Ju,16Ja)
Q. Write down the urinary findings in a patient with nephritic syndrome. (DU-16Ju, SMU-23M,19Nv)
Q. Short note: Nephritic syndrome (AGN). (CU-04S)
Ans.
Nephritic syndrome / AGN: Nephritic syndrome or acute glomerulonephritis (AGN) is a **glomerular disease** of kidney which is characterized by **inflammation in the glomeruli** and is manifested as **haematuria** (red blood cells and red cell casts in urine), **proteinuria** (usually subnephrotic range) with or without **edema, azotemia** and **hypertension.**

(Ref: Robbins/10th/906)

Causes of nephritic syndrome (AGN): ***(Very Important for VIVA)***

A. PRIMARY GLOMERULAR DISEASES:

1. **Acute proliferative glomerulonephritis:**
   1. ***Post-streptococcal glomerulonephritis*** (Group A β-hemolytic streptococcus)
   2. ***Non-streptococcal acute glomerulonephritis*** (post-infectious glomerulonephritis)
      - **Bacterial:** Staphylococcal endocarditis, pneumococcal pneumonia, meningococcaemia.
      - **Viral:** Hepatitis-B & C virus, mums, HIV, varicella, infectious mononucleosis.
      - **Parasitic:** Malaria, toxoplasmosis.
2. Rapidly progressive (crescentic) glomerulonephritis (RPGN)
3. Membranoproliferative glomerulonephritis

4. IgA nephropathy

B. SYSTEMIC DISEASES:

1. Goodpasture syndrome (pulmonary hemorrhage associated with renal failure)
2. SLE (Lupus nephritis)
3. Polyarteritis nodosa
4. Wegener granulomatosis (granulomatosis with polyangiitis)
5. Microscopic polyangiitis
6. Henoch-Schönlein purpura
7. Cryoglobulinaemia.

(Ref: Robbins/10th/906; Harsh Mohan/7th/648)

Diagnosis of nephritic syndrome (AGN):

1. **Clinical features:**
   i) Patient is usually a child of 5-10 years of age
   ii) Haematuria (brown urine)
   iii) Edema and generalized fluid retention
   iv) Hypertension
   v) Oliguria
   vi) Evidence of sore throat or skin infection

(Ref: Davidson's/23rd/392)

2. **Laboratory investigations:**
   a. **Routine and microscopic examination of urine:**
      - **Volume:** Reduced to 200-400 ml/day (oliguria).
      - **Colour:** High coloured (dark red or smoky).
      - **Specific gravity:** Usually high.
      - **Reaction:** Acidic.
      - **Protein:** + / ++ (moderate amount).
      - **RBC:** Plenty.
      - **Epithelial & pus cell:** Present (few)
      - **Cast:** RBC cast & granular cast.
   b. **24 hour urinary protein estimation:** < 3.5 gm / 24hrs.
   c. **Blood:** TC, DB, Hb%, ESR.
   d. **Blood urea, serum creatinine:** may be raised.
   e. **Serum electrolytes:** ↑K+, ↓Na+.
   f. USG of KUB region to see both kidneys present or not, kidney size, position, any growth
   g. Renal biopsy.
   h. **Bacteriological test:**
      - Throat swab, swab from skin lesion for Gram straining & C/S.
      - **ASO titre:** ↑ in streptococcal infection.

(Ref: Prof. Khaleque/204; Lecture SSMC)

Q. Write down the urinary findings in nephrotic syndrome. (DU-12Ja, SMU-23M,10Ja)
Q. Mention the urinary findings in nephritic syndrome / AGN. (DU-11Ju, SMU-23M)
Q. How can you differentiate nephritic and nephritic syndrome by examining urine? (CU-19Nv, RU-12Ju)
Q. What are the lab investigations that may help to differentiate nephrotic syndrome from nephritic syndrome? (DU-04J)

Q. Give the biochemical changes and urinary findings of nephritic and nephrotic syndrome. (DU-18M)

Q. Give the urinary findings in nephritic and nephrotic syndrome. (DU-16Ju, SMU-23M,21/19Nv,17M, CU-20M, RU-11Ju)

Q. What are the expected urinary findings in AGN? (DU-10Ju,06Ja)

Q. Short note: Urinary findings in nephrotic syndrome. (CU-16Ju)

Ans.

Urinary findings in AGN & nephrotic syndrome:

Examination	Nephritic syndrome (AGN)	Nephrotic syndrome
A. Physical		
1. Amount of urine	Markedly reduced (200-400 ml/day)	Reduced
2. Colour	High coloured (dark red or smoky)	Normal colour
3. Odour	Normal	Normal
4. Specific gravity	High	Normal / high.
B. Chemical		
1. Reaction	Acidic	Acidic
2. Albumin	+/++ (moderate)	+++ /++++ (massive)
C. Microscopic		
1. RBC	Plenty	+ / -
2. Cast	RBC cast and granular casts may be present	Hyaline casts may be present
3. Epithelial cell & pus cell	May be present	May be present
4. Organism	Absent	Absent

(Ref: Prof. Khaleque/204; Lecture SSMC)

Q. A boy of 7 years developed peri-orbital edema with high coloured scanty urination, following a history of sore throat, 3 weeks back. What is your clinical diagnosis? What do you expect in microscopic findings of this urine? (DU-14Ja)

Ans.

Clinical diagnosis: AGN.

Microscopic findings of urine: *Please write from above.*

Q. A boy of 15 years has presented with fever, peri-orbital edema, and oliguria. What is your provisional diagnosis? What are the possible urinary findings in this case?

Ans.

Provisional diagnosis: AGN.

Urinary findings: *Please write from above.*

Nice to Know:

Characteristics of edema in different disease:

- **Nephrotic syndrome**—edema is generalized. It starts in face, and then involves whole body. May be ascites, bilateral pleural effusion, pericardial effusion, etc. due to hypoalbuminemia.
- **Congestive cardiac failure**—edema starts in leg (dependent edema). In severe, advanced case, there may be ascites, swelling of face.

- **Cirrhosis of liver**—first there is ascites, then may be edema in leg.
- **Malnutrition or hypoproteinemia**—edema of the feet and face, later may be ascites or even generalized.

(Ref: Long Cases in Clinical Medicine/1st/378)

Causes of puffy face:

1) Renal cause—nephrotic syndrome, acute glomerulonephritis
2) Myxedema
3) Cushing's syndrome
4) SVC obstruction
5) Angioneurotic edema
6) Hypoproteinemia
7) Congestive cardiac failure in advanced stage
8) Alcoholism
9) Acromegaly.

(Ref: Long Cases in Clinical Medicine/1st/377)

Disorders of Urine Volume

Q. Short note: Anuria.

Ans.

Anuria: Anuria is the (almost) total absence of urine (**<100 ml/day**).

(Ref: Davidson's/23rd/391; Lecture SSMC)

Causes of anuria:

1. **Pre-renal causes:**
   - Traumatic shock
   - Severe hemorrhage
   - Extensive burns
   - Dehydration from vomiting, diarrhoea etc.
   - Spinal anaesthesia
2. **Renal causes:**
   - Acute tubular necrosis
   - Acute glomerulonephritis (AGN)
   - Bilateral pyelonephritis
   - Vascular thrombosis
3. **Post-renal causes:**
   1. Urinary tract obstruction due to urinary calculi and prostatic enlargement etc.

(Ref: Davidson's/23rd/391; Prof. Khaleque/201; Lecture SSMC)

Q. Define oliguria. (DU-18M,14Ju) **Write down the causes of oliguria.** (DU-18M,14Ju, CU-08Ju)

Q. Short note on: Oliguria. (DU-04M)

Ans.

Oliguria: When urinary output is **less than 400 ml/day**, it is called oliguria.

(Ref: Lecture SSMC; Davidson's/23rd/391; Prof. Khaleque/201)

Causes of oliguria:

1. **Pre-renal causes:**
   - Dehydration from vomiting, diarrhoea, or excessive sweating
   - Shock

- Cardiac failure
- Severe hemorrhage
- Extensive burns

2. **Renal causes:**
   - Acute tubular necrosis
   - Acute glomerulonephritis (AGN)
   - Nephrotic syndrome

3. **Post-renal causes:**
   - Urinary tract obstruction due to urinary calculi and prostatic enlargement etc.

(Ref: Davidson's/21st/475; Prof. Khaleque/201; Lecture SSMC)

Q. Short note: Polyuria.

Ans.

Polyuria: Polyuria is defined as a urine volume in excess of 3 L/24 hrs.

(Ref: Davidson's/23rd/396; Lecture SSMC)

Causes of polyuria:

1. Excess fluid intake
2. Osmotic diuresis: hyperglycaemia, hypercalcaemia
3. Cranial diabetes insipidus
4. Nephrogenic diabetes insipidus:
   - Rare inherited mutations in vasopressin receptor or aquaporin 2 genes
   - Lithium
   - Diuretics
   - Interstitial nephritis
   - Hypokalaemia
   - Hypercalcaemia.

(Ref: Davidson's/23rd/396)

Haemoglobinuria

Q. Short note: Haemoglobinuria. (RU-12Ja)

Ans.

Haemoglobinuria: Presence of haemoglobin in urine due to ***excessive intravascular haemolysis***, is called haemoglobinuria. Occult blood test will be positive.

(Ref: Prof. Khaleque/202)

Causes of haemoglobinuria:

A) **Acute haemoglobinuria:**
1. Incompatible blood transfusion
2. Haemolytic anaemia due to drugs and chemicals
3. 'Black water fever' in malignant malaria
4. Favism
5. Paroxysmal cold heamoglobinuria
6. March haemoglobinuria
7. Haemolytic anaemia due to infections (mainly *Clostridium welchii*)
8. Haemolytic anaemia associated with eclampsia
9. Haemolytic-uraemic syndrome
10. Haemolytic anaemia due to burns
11. Snake and spider bites

B) Chronic haemoglobinuria:

1. Paroxysmal nocturnal haemoglobinuria
2. Cardiac haemolytic anaemia
3. Cold haemagglutinin disease.

(Ref: de Gruchy/5th/178; Prof. Khaleque/202)

Chyluria

Q. What is chyluria? (RU-17Nv/Ja,14Ja,09Ju)

Q. Short note on: Chyluria. (RU-17/14Ja,09Ju)

Ans.

Chyluria: When chyle is present in urine, it is called *chyluria*.

Causes:

1. ***Filariasis***
2. Diabetes mellitus
3. Kidney tumors
4. Fracture of long bones.

(Ref: Prof. Khaleque/202)

Pyuria

Q. Short note: Pyuria.

Ans.

Pyuria: Presence of large number of pus cells in urine is called *pyuria*.

Causes:

1. Urinary tract infection (UTI)
2. Renal tuberculosis (***sterile pyuria*** – pus cells but no organism in urine)
3. Renal stone.

Q. Mention causes of sterile pyuria. (RU-16Ju)

Ans.

Sterile pyuria: Neutrophils (pus cells) are present in the urine but routine urine culture may be negative.

Causes of sterile pyuria:

- Renal tuberculosis
- Patient of UTI with antibiotic
- AGN.

(Ref: Davidson's/23rd/430; Lecture SSMC & DMC)

Urinary Tract Infection (UTI)

Q. What is UTI?

Ans.

Urinary tract infection (UTI): UTI is defined as the presence of $>10^5$ organisms/ml urine in the urinary tract in a midstream sample of urine (MSU).

Q. What are the causes of UTI?

Ans.

Causes of UTI: Organisms causing UTI in the community include-

- *Escherichia coli* derived from the gastrointestinal tract (about 70% of infections)

- Proteus
- *Staphylococcus saprophyticus* or *Staph. epidermidis*
- *Enterococcus fecalis*
- *Pseudomonas species*
- *Klebsiella spp.*

(Ref: Kumar & Clark/10th/1381)

Q. Write down the urinary findings of UTI. (BUP-16Ja)

Ans.

Investigations of UTI:

1. Routine examination of urine: Pyuria, haematuria.
2. Culture of clean catch mid-stream sample of urine or urine obtained by supra-pubic aspiration.
3. Full blood count.
4. Blood urea, serum electrolytes, serum creatinine.
5. Blood culture.
6. Renal ultrasound or CT (if pyelonephritis is suspected).
7. Cystoscopy - To evaluate continuous haematuria or other suspicion of bladder lesion.

Q. Write down the treatment of UTI. (BUP-18Nv)

Ans.

Treatment of UTI: Please write from "arif's representation on PHARMACOLOGY & THERAPEUTICS.

Q. A 27 year old male presented with increased frequency of micturition. (CMU-22Nv)

a) **What is your possible diagnosis?**
b) **What are the possible causes of it?**
c) **What are the lab tests and positive findings to establish the diagnosis?**

Ans.

a) **Possible diagnosis:** UTI.

b) **Causes of UTI:** *Please see above.*

c) **Lab. tests with findings:**
   - **Urine RME:** Pyuria, haematuria.
   - **Urine culture and sensitivity:** To find out the causative organism.
   - **Complete blood count with ESR:** Neutrophilic leukocytosis, raised ESR.

Q. A 40 years male presented with right flank colicky pain with haematuria. (CMU-22M)

a) **What is your possible diagnosis?**
b) **What are the possible causes of it?**
c) **What are the laboratory tests and positive findings to establish the diagnosis?**

Ans.

a) **Possible diagnosis:** UTI.

b) **Possible causes:** *Please see above.*

c) **Lab. tests with positive findings:** *Please see above.*

Q. A young lady of 22 years presented with fever dysuria & lower abdominal pain. Her urinary examination revealed numerous pus cells. (BUP-18Nv)
What is your diagnosis?
What are the laboratory investigations required for the confirmation of the diagnosis and treatment?
Ans.
Diagnosis: UTI.

Laboratory investigations & treatment: *Please see above.*

Classification of DM:

A. Type 1 diabetes (T1D) *(β-cell destruction, usually leading to absolute insulin deficiency)*
- Immune-mediated
- Idiopathic (autoantibody-negative)

B. Type 2 diabetes (T2D) *(combination of insulin resistance and β-cell dysfunction)*

C. Other types:

1. Genetic defects of β-cell function
- Maturity-onset diabetes of the young (MODY)
- Neonatal diabetes
- Maternally inherited diabetes and deafness (MIDD)
- Defects in proinsulin conversion
- Insulin gene mutations

2. Genetic defects in insulin action
- Type A insulin resistance
- Lipoatrophic diabetes

3. Exocrine pancreatic defects ("pancreatogenic" or type 3C diabetes)
- Pancreatitis
- Pancreatectomy/ trauma
- Pancreatic cancer
- Cystic fibrosis
- Haemochromatosis
- Fibrocalculous pancreatopathy

4. Endocrinopathies:
- Acromegaly
- Cushing syndrome
- Hyperthyroidism
- Pheochromocytoma
- Glucagonoma

5. Infections:
- Cytomegalovirus
- Coxsackie B virus
- Congenital rubella

6. Drugs:
- Glucocorticoids
- Thyroid hormone
- Interferon-α
- Protease inhibitors
- β-adrenergic agonists
- Thiazides
- Nicotinic acid
- Phenytoin (dilantin)
- Vacor

7. Genetic syndromes associated with diabetes:
- Down syndrome
- Kleinfelter syndrome
- Turner syndrome
- Prader-Willi syndrome

8. Gestational diabetes mellitus.

(Ref: Robbin's/10th/1099; Davidson's/23rd/733)

CHAPTER 03

BLOOD GLUCOSE AND DIABETES MELLITUS

Must to Know:

Blood glucose levels: ***(Very Important for VIVA)***

Normal:

Fasting: 3.6-6.1 mmol/L (65-110 mg/dl)

Random & 2 hours postprandial: <7.8 mmol/L (<140 mg/dl)

Impaired glucose tolerance (IGT):

Fasting: 6.1-6.9 mmol/L. (110-125 mg/dl)

Random & 2 hours post prandial: 7.8-11.0 mmol/L (140-199 mg/dl)

Diabetes mellitus (DM):

Fasting: ≥ 7.0 mmol/L (≥126 mg/dl)

Random & 2 hours postprandial: ≥ 11.1 mmol/L (≥ 200 mg/dl).

(Ref: Davidson's/23rd/726)

Q. What is diabetes mellitus? (DU-22M,17Ja,08Ju, BUP-22Nv/M,21Nv/M, CMU-22Nv,05Ja, RU-18Ja) **Classify diabetes mellitus.** (DU-22M,17Ja,14Ju, CMU-22Nv)

Q. Mention the risk factors of diabetes mellitus. (BUP-21Nv/M)

Ans.

Diabetes mellitus (DM): Diabetes mellitus is a clinical syndrome characterised by an increase in plasma blood glucose (**hyperglycaemia**) due to **absolute** or **relative deficiency of insulin**.

(Ref: Davidson's/23rd/722)

Or,

Diabetes mellitus is a group of **metabolic disorders** sharing the common feature of **hyperglycemia** caused by defects in **insulin secretion, insulin action**, or, mostcommonly, **both**.

(Ref: Robbins/10th/1097)

Q. What are the clinical features of a diabetes patient? (DU-03Ja)
Q. How will you diagnose / confirm a case of diabetes mellitus in a pathology laboratory? (CMU-22Nv,18M, SU-17M,04Ja)
Q. How will you confirm a case of diabetes mellitus? (RU-17Ja)
Q. Write down the methods you will use in the diagnosis of diabetes mellitus. (RU-14/13/11Ja)
Q. Write down the laboratory diagnosis of diabetes mellitus. (CU-20Ju, RU-17Nv/Ju,16Ja)
Q. Give your approach to diagnose a case of diabetes mellitus. (RU-18Nv)

Ans.

Diagnosis of diabetes mellitus: The term diagnosis refers to confirmation of diabetes in people who have symptoms, or who have had a positive screening test.

A. Patient complains of symptoms suggesting diabetes:

Common:
1. Polyuria *(frequent micturition)*
2. Polydipsia *(increased thirst)*
3. Ploy**p**hagia *(increased appetite)*
4. Tachycardia
5. Weakness
6. Weight loss

Others:
1. Dehydration
2. Hypotension
3. Hypothermia
4. Confusion
5. Drowsiness
6. Hyperventilation
7. Muscle wasting
8. Acidosis & coma.

(Ref: Lippincot's/5th/337; Ganong/24th/449)

B. Laboratory investigations in DM:

1. **Fasting, random and post-prandial blood glucose concentration:** Diagnosis is confirmed by-
   - **Fasting** blood glucose ≥7.0 mmol/l (≥126 mg/dl)
   - **Random** blood glucose ≥11.1 mmol/l (≥200 mg/dl)
   - **Post-prandial** blood glucose (2 hrs after meal) ≥11.1 mmol/l (≥200 mg/dl)

   In asymptomatic patients *two* samples are required to confirm diabetes.

2. **Oral glucose tolerance test (OGTT):**
   - Fasting plasma glucose ≥7.0 mmol/l (≥126 mg/dl)
   - 2 hours after 75 gm glucose load ≥11.1 mmol/l (≥200 mg/dl)

   Indications for *oral glucose tolerance test*: (Impaired glucose tolerance)
   - Fasting plasma glucose 6.1-6.9 mmol/l (110-125 mg/dl)
   - Random plasma glucose 7.8-11.0 mmol/l (140-199 mg/dl)

3. **Urine testing** for glucose, ketone bodies, and proteins

4. **Glycosylated Hb (HbA_1c):**
   - Normally 4-6% of total Hb are glycosylated
   - Diagnosis of diabetes is confirmed by HbA1c ≥ 48 mmol/mol

5. **Other investigations:**
   - A full blood count

- Fasting lipid profile
- Blood urea and serum creatinine
- Serum electrolytes.

(Ref: Davidson's/23rd/726)

Nice to Know:
Random means without regard to time since the last meal.
Fasting means no calorie intake for 8 hours at least (not more than 16 hours).
(Ref: Long Cases in Clinical Medicine/1st/610)

Q. Write the diagnostic criteria for diabetes mellitus (as per ADA & WHO). (CMU-22M,21/20Nv)
Q. Give the WHO diagnostic criteria for diagnosis of diabetes mellitus. (DU-23Nv,21Ja,20Nv/M,19Nv,14/07Ju, BUP-22Nv,21Nv/M, CU-20M, RU-12Ja)
Ans.
Diagnostic criteria for diabetes mellitus (as per ADA & WHO): ***(Very Important for VIVA)***

1. A single **fasting plasma glucose** ≥ 7.0 mmol/L (≥126 mg/dl) in symptomatic patients and on two separate occasions in asymptomatic patients.
2. A **random plasma glucose** ≥ 11.1 mmol/L (≥ 200 mg/dl) in an individual with classic sign/ symptoms of diabetes (polyuria, polydipsia, polyphagia & weight loss) and on two separate occasions in asymptomatic patients.
3. A **2 hours OGTT** ≥ 11.1 mmol/L (≥ 200 mg/dl) after a 75 gm load of glucose.
4. An **HbA1c** of ≥ 48 mmol/mol (≥ 6.5%) is also diagnostic of diabetes.

(Ref: Lecture SSMC; Davidson's/23rd/727)

(N.B: As HbA1c reflects the last 2–3 months of glycaemia, it should not be used to diagnose diabetes where the duration of onset is short, i.e. in someone with suspected type 1 diabetes or severe symptomatic hyperglycaemia.)

(Ref: Davidson's/23rd/727)

Q. Mention the criteria of the patients who should be considered for diabetic testing.
Ans.
Criteria of the patients who should be considered for diabetic testing:

1. All individuals 45 years of age or older (repeat at 3 years interval)
2. Persons with classic signs & symptoms of diabetes (polyuria, polydipsia, ploy**p**hagia & weight loss)
3. Obesity
4. History of 1st degree relations with diabetes
5. Women with gestational diabetes
6. Individuals with hypertension (> 140/90)
7. An HDL cholesterol level less than or equal to 35 mg/dl or TG level greater than or equal to 250 mg/dl.
8. Presence of impaired glucose tolerance on previous testing.

(Ref: Lecture SSMC)

Q. Write down the confirmatory biochemical tests for diabetes mellitus.
Ans.
Confirmatory biochemical tests for diabetes mellitus:

- Either **fasting plasma glucose (FPG)** or **random plasma glucose (RPG)** can be used for the **confirmation** of diagnosis. In *symptomatic* individuals one abnormal plasma glucose measurement in the diabetic range confirms the diagnosis.

- *Asymptomatic* individuals with a positive screening test (FPG or RPG) need another abnormal plasma glucose measurement on another day for the confirmation of the diagnosis.
- OGTT is not recommended for routine use as a confirmatory test.

(***N.B:*** **Fasting** is defined as no caloric intake for at least 8 h. **Random** is defined as any time of day without regard to time since last meal.)

(Ref: Manual of diabetes mellitus)

Nice to Know:

Screening tests for DM:

- *Screening is recommended for all individuals with one or more major risk factors for developing diabetes mellitus*
- *FPG (fasting plasma glucose) is the laboratory test recommended for screening of individuals for diabetes mellitus*
- *RPG (random plasma glucose) is an alternative test for screening.*
- *When facilities to do FPG or RPG are not available, CBG (capillary blood glucose) and UG (urinary glucose) are alternatives screening for patients with classical symptoms of DM.*

(Ref: Manual of diabetes mellitus)

Q. What are the metabolic goals of management of diabetes mellitus? (CU-11Ju)

Ans.

Metabolic goals of management of diabetes mellitus:

1. **Target blood glucose level:** Fasting blood glucose < 6 mmol/L.
2. **Target HbA_1C: ≤7%**
3. **Target levels of blood lipids:**
   - Total cholesterol: < 5.0 mmol/L (approx. 190 mg/dl)
   - LDL cholesterol: < 3.0 mmol/L (approx. 115 mg/dl).

Q. What is hyperglycaemia? (DU-12Ju) **What are the causes of hyperglycaemia?** (SUST-21/19Nv, RU-20Nv)

Q. Mention the important causes (any 4) of hyperglycaemia. (DU-05M, RU-17Ja, CU-18M,16/14Ja,11/10Ju,11/09Ja, SU-17M,16Ja,15/13Ja,09Ju)

Q. Mention the hyperglycaemic conditions.

Ans.

Hyperglycaemia: Hyperglycaemia is a condition when blood sugar level is raised above normal.

Causes of hyperglycaemia:

1. Diabetes mellitus
2. Impaired glucose tolerance
3. Pregnancy
4. Pancreatic diseases e.g. pancreatitis, haemochromatosis, pancreatectomy.
5. Liver disease
6. Endocrine disorders e.g. thyrotoxicosis, Cushing's syndrome, acromegally, pheochromocytoma.
7. Drugs e.g. corticosteroids, thiazide diuretics, phenytoin.

(Ref: Prof. Khaleque/191)

Q. What is hyperglycaemia sine glycosuria? (DU-08Ju, RU-07Ja)

Q. Why sugar is absent in urine during hyperglycaemia sine glycosuria? (DU-22Nv,21Oct/M)

Q. Write about hyperglycaemia sine glycosuria. (RU-19M)

Q. Short note: Hyperglycaemia sine glycosuria. (DU-09Ju, CU-11Ju; RU-16Ja,14Ju,12Ja,10Ju)

Ans.

Hyperglycaemia sine glycosuria: This is a condition in which the plasma glucose is above the normal renal threshold for glucose (180 mg/dl), but the urine is free from glucose.

Cause: This is due to **raised renal threshold above normal.** This may occur in **uncontrolled diabetes mellitus.**

(Ref: Prof. Khaleque/191)

Q. In which disease blood glucose normal but there is glucose in urine? ***(Very Important for VIVA)***

Ans.

Renal glycosuria (Reverse of hyperglycaemia sine glycosuria).

Q. A diabetic patient has blood glucose level more than 200 mg/dl, but he has no glycosuria. How it can be possible? ***(Very Important for VIVA)***

Ans.

Hyperglycaemia sine glycosuria.

Q. Enumerate the causes of hypoglycaemia. (RU-17/15Ja, CU-13Ju/Ja)

Q. Short note: Hypoglycaemia. (CU-16Ju)

Ans.

Hypoglycaemia: Hypoglycaemia is the condition when blood glucose level is reduced below normal (<2.2 mmol/L).

Causes of hypoglycaemia: ***(Very Important for VIVA)***

1. ***Diabetic patient taking anti-diabetic drugs*** with delayed, inadequate or missed meal, heavy exercise or alcohol
2. Overdose of hypoglycaemic drugs such as insulin or sulphonylurea drug
3. Addison's disease
4. Insulin-secreting tumour, e.g. ***insulinoma,*** retroperitoneal fibrosarcoma etc.
5. Malnutrition
6. Severe liver disease
7. ***Malabsorption,*** e.g. coeliac disease
8. Gastroparesis due to autonomic neuropathy
9. Breast-feeding by diabetic mother.

(***N.B:*** Remember: **AMI: A** → Anti-diabetic drugs; **M** → Malabsorption; **I** → Insulinoma).

Clinical features:

1. **Neuroglycopenic:**
   - Confusion
   - Drowsiness
   - Speech difficulty
   - Inability to concentrate
   - Irritability
   - Incoordination
2. **Autonomic:** Sweating, trembling, hunger, anxiety.
3. **Non-specific:** Nausea, headache, tiredness.

(Ref: Davidson's/21st/812,813)

Q. A old man aged 50 years presented with polydipsia, polyphagia and polyuria. What could be the probable diagnosis? How will you establish your diagnosis? (RMU-22M)
Ans.
Probable diagnosis: Diabetes mellitus.

Laboratory investigations and diagnostic criteria: *Please write from above.*

Glycosuria

Q. What is glycosuria? (CU-04Ja) **Enumerate the causes of glycosuria.** (RU-20M,17Nv/Ju, 16/14/13/11/07Ja, CU-14Ju,07Ja, SU-11Ju)
Q. What is renal glycosuria? (DU-11Ja)
Q. Short note: Renal glycosuria. (BUP-22M, RU-14Ju, SU-12Ja)
Q. Short note: Alimentary glycosuria. (DU-18Ja, RU-13/10Ja)
Ans.
Glycosuria: Presence of **glucose in urine** which can be detected by conventional method (Benedict test) is called glycosuria.

(Ref: Prof. Khaleque/202)

Causes:

1. **Untreated diabetes mellitus (DM)**
2. **Renal glycosuria:** Blood glucose values are **normal** but **sugar is present in urine** due to **low renal threshold** value for glucose.

   In renal glycosuria, there is reduced rate of reabsorption of glucose by kidney tubules as occur in **serious tubular damage** or **inherited defect in tubular absorption**.
3. **Alimentary (lag storage) glycosuria:** Glycosuria developing after ingestion of a moderate amount of sugar or starch *(which normally is dissipated without appearing in the urine)* because the **rate of intestinal absorption exceeds** the capacity of the liver and the other tissues to remove the glucose, thus allowing blood glucose levels to become high enough for renal excretion to occur {**above renal threshold** (10 mmol/l or 180 mg/dl) value}.

   This may occur in-
   - Normal people
   - Liver disease
   - Hyperthyroidism
   - After gastric surgery (gastrectomy & vagotomy)
4. **Fanconi syndrome:** Glucose, amino acid, phosphate are excreted due to impaired absorption.
5. **Sometimes during pregnancy.**

(Ref: Lecture SSMC; Prof. Khaleque/192)

Q. Why sugar is present in renal glycosuria? (DU-23Nv)
Ans.
Sugar is present in renal glycosuria: In renal glycosuria, blood glucose values are **normal** but **sugar is present in urine** due to **low renal threshold** value for glucose.

Nice to Know:

Raised renal threshold for glucose occurs in-

1. Heart failure
2. Shock
3. Na^+ depletion.

(Ref: Lecture SSMC)

Q. How will you differentiate diabetes mellitus from renal and alimentary glycosuria?

Ans.

Differences of diabetes mellitus from renal and alimentary glycosuria:

Diabetes mellitus	Renal glycosuria	Alimentary glycosuria
1. Hyperglycaemia present	Hyperglycaemia absent	Transient hyperglycaemia (due to increased absorption) present
2. Renal threshold value of sugar normal	Renal threshold value of sugar below normal	Renal threshold value of sugar normal
3. Ketosis present	Ketosis absent	Ketosis absent
4. Caused by disease of the pancreas	Caused by diseases of the kidney	Found in ▪ Liver disease ▪ Hyperthyroidism ▪ After gastric surgery (gastrectomy & vagotomy).

Oral Glucose Tolerance Test (OGTT)

Q. What do you mean by OGTT? (DU-22Nv,21Oct/M,11Ja, BUP-22Nv, SU-20M) **Discuss the interpretation of OGTT.** (DU-11Ja, SUST-21Nv,20M,19Nv,15/13Ja,11Ju, RU-18M,16Ju, CU-14Ja,10Ju/Ja)

Q. How can you confirm OGTT? (DU-15Ja)

Q. Enumerate indications of glucose tolerance test (GTT)/OGTT. (RU-19Nv,18M,07Ja)

Q. Briefly describe the procedure of oral glucose tolerance test (OGTT). (SU-20M,19Nv, RU-16Ju,10Ja, CU-15/14Ju,12/09Ja)

Q. Write down the procedure & interpretation of OGTT. (DU-22Nv,21Oct/M,18Nv,17M,06S/Ja, SU-16Ja, CU-08Ju,07/05Ja, RU-15/12/08Ju)

Q. How will you prepare a patient for OGTT? (SU-22Nv)

Q. Draw different types of diabetic curves. (DU-09Ja)

Q. Draw & level different glucose tolerance curves with interpretation. (RU-10Ja, SU-10/09Ju)

Q. Draw & label the different types of diabetic / GTT curves with interpretations. (CU-08Ja)

Q. Short note: GTT / OGTT. (DU-05S/Ja,04Ja, SU-22/19M,14Ju,06Ja,05M, RU-17M)

Q. Short note: OGTT and its interpretation. (DU-13Ju)

Q. Short note: Interpretation of OGTT curves. (SU-12Ju)

Q. Short note: GTT curves. (DU-16Ja)

Ans.

Oral glucose tolerance test (OGTT/ GTT): It is a laboratory test to diagnose diabetes mellitus. When random blood glucose values are elevated but are not diagnostic of diabetes, glucose tolerance is usually assessed by the glycemic response to oral ingestion of a glucose load.

It measures the ability of the body to tolerate, or cope with standard dose of glucose. Tolerance is reduced when insulin is insufficient or absent.

Indication of OGTT: Patients with-

a. **Fasting plasma glucose :** 6.1-6.9 mmol/L (110-125 mg/dl)
b. **Random plasma glucose:** 7.8-11.0 mmol/L (140-199 mg/dl)

(Ref: Davidson's/23rd/726)

Preparation of the patient:

1. Unrestricted CHO diet (minimum 150 mg/day) for 3 days before test
2. Avoidance of drug affecting blood glucose level (e.g. corticosteroid, oral contraceptives etc.)
3. Treatment of any infection (if present)
4. Fasted overnight (for at least 8 hours) prior to the test
5. Avoidance of smoking & exercise prior to the test
6. Rest before test (for at least 30 minutes)
7. The person should sit throughout the procedure
8. No smoking is permitted during test interval
9. Caffeinated beverages should not be consumed
10. The person should not be bed-ridden or under stress.

Procedure:

1. Fasting venous blood for plasma and corresponding urine sample is collected.
2. 75 gm glucose dissolved in 250-300 ml of water is given by mouth within 5 minutes of fasting sample collection.
3. Venous blood and urine samples are collected 2 hours after 75 gm glucose load or at half hourly intervals for at least two hours.
4. Plasma glucose on each blood sample and sugar on each urine sample is estimated.

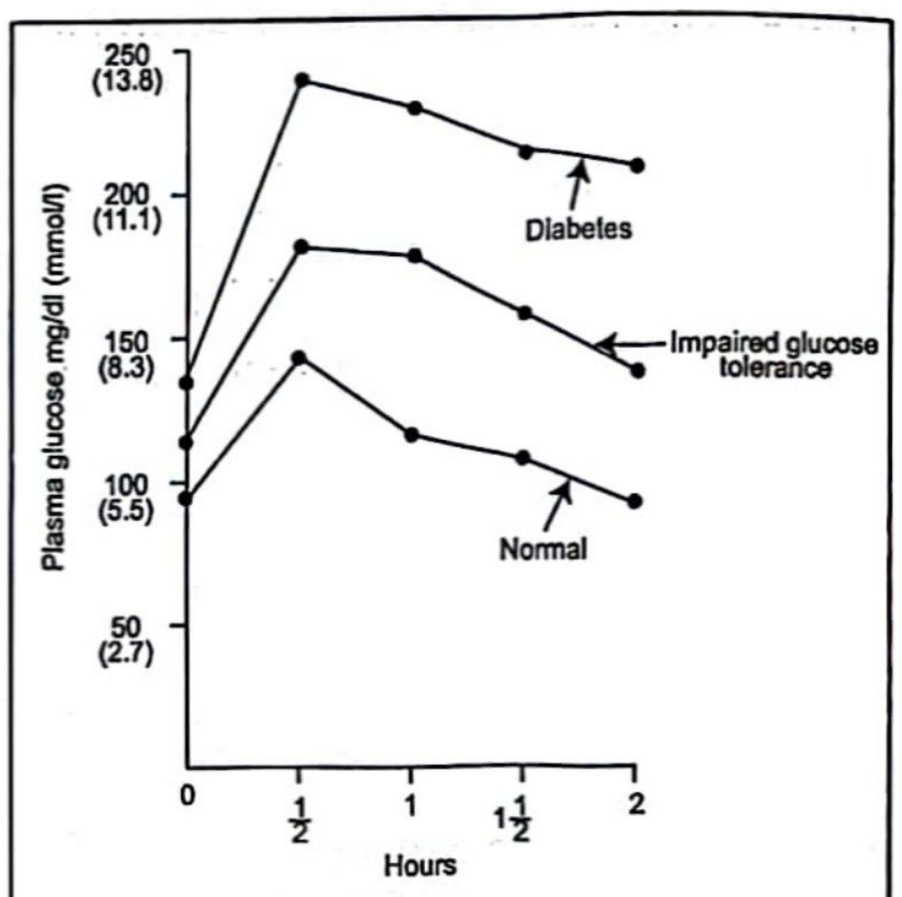


Fig : Oral glucose tolerance test.

Interpretation of OGTT curve:

Healthy	Fasting	3.6-6.1 mmol/L (65-110 mg/dl)
	2 hrs after 75 gm glucose load	<7.8 mmol/L (<140 mg/dl)
Diabetic	Fasting	≥7.0 mmol/L (≥126 mg/dl)
	2 hrs after 75 gm glucose load	≥11.1 mmol/L (≥200 mg/dl)
Impaired glucose tolerance (IGT)	Fasting	6.1-6.9 mmol/L (110-125 mg/dl)
	2 hrs after 75 gm glucose load	7.8-11.0 mmol/L (140-199 mg/dl)

(***N.B***: For asymptomatic patients, 2 abnormal values greater than 11.1 mmol/l are needed to establish diagnosis of DM.)

(Ref: Davidson's/23rd/726)

Nice to Know:

- *In OGTT, **testing of urine for glucose** in all the samples is the usual procedure for detecting DM, but it has **no diagnostic value** because DM may exist without glycosuria if blood glucose level does not exceed the renal threshold.*
- *Sometimes mere may be **glycosuria in absence of DM**, e.g. renal glycosuria, alimentary glycosuria.*
- ***Glycosuria** frequently coexists **with DM**, but for diagnosis of DM glycosuria is not mandatory.*

Q. Write down the importance of glucose tolerance test.

Ans.

Importance of glucose tolerance test:

1. To find out the ability of the body to carbohydrate metabolism
2. To detect-
   - Diabetes mellitus
   - Endocrine dysfunction
   - Renal glycosuria
   - Alimentary glycosuria.

Q. How will you prepare a patient for OGTT? (SU-22Nv, CU-11Ja)

Ans.

Preparation of a patient for OGTT:

- Unrestricted CHO diet (minimum 150 mg/day) for 3 days before test
- Avoidance of drug affecting blood glucose level (e.g. corticosteroid, oral contraceptives etc.)
- Treatment of any infection (if present)
- Fasted overnight (for at least 8 hours) prior to the test
- Avoidance of smoking & exercise prior to the test
- Rest before test (for at least 30 minutes)
- The person should sit throughout the procedure
- No smoking is permitted during test interval
- Caffeinated beverages should not be consumed
- The person should not be bed-ridden or under stress.

Nobody will pass at VIVA without pinpoint explanation of the OGTT interpretation

Impaired Glucose Tolerance (IGT)

Q. Short note: Pre diabetes. (*Very Important for VIVA*)

Ans.

Pre diabetes: It is the intermediary metabolic stage of glucose between normal glucose homeostasis and diabetes mellitus.

Components (types):

1. IFG (impaired fasting glucose)
2. IGT (impaired glucose tolerance)

Laboratory diagnosis: It is done by OGTT (WHO criteria)-

Fasting glucose (mmol/L)	2 hrs after OGTT (mmol/L)	Diagnosis
6.1 - 6.9	<7.8	IFG
6.1 - 6.9	7.8 - 11.0	IGT

Consequence / importance:

1. Pre diabetics are at risk of developing diabetes mellitus (DM) later
2. Pre diabetics are at increased risk of vascular complications
3. It is a useful cautionary clinical message to decide on preventive measures through dietary and lifestyle modification to avoid development of DM.

Q. What is IFG? (DU-15Ja,13Ju)

Q. Short note: Impaired fasting glucose (IFG). (*Very Important for VIVA*)

Ans.

Impaired fasting glucose (IFG): Impaired fasting glucose (IFG) refers to a condition in which the fasting blood glucose level is consistently elevated above what is considered normal levels; however, it is not high enough to be diagnosed as diabetes mellitus.

Or,

IFG is defined as the fasting glucose level between 6.1 to 6.9 mmol/L (110 to 125 mg/dL) according to WHO.

Diagnostic criteria: The WHO criteria for impaired fasting glucose (IFG) -

- Fasting plasma glucose = 6.1 mmol/L (110 mg/dL) to 6.9 mmol/L (125 mg/dL)
- 2 hrs after OGTT glucose is normal, i.e. <7.8 mmol/L (<140 mg/dl).

Importance:

1. These patients are prone to develop frank diabetes mellitus and cardiovascular disease.
2. There is a 50% risk over 10 years of progressing to overt diabetes.
3. IFG is a risk factor for mortality due to the serious complications of type-2 diabetes mellitus.

Advice to patients with IFG: The patients are advised for weight reduction about 5 to 10% of their body weight, regular exercise and follow up. Usually no drug therapy is recommended.

(Ref: Lecture SSMC; Long Cases in Clinical Medicine/1st/610)

Q. Q. What is IGT? (DU-15Ja,13Ju) **Mention the clinical importance of IGT.** (CU-11Ju)
Q. What will be the OGTT findings in IGT? (SU-14Ju)
Q. Write the diagnostic criteria for defining impaired glucose tolerance test. (CMU-21M)
Q. Short note: Impaired glucose tolerance (IGT). (DU-15Ju,12Ja) ***(Very Important for VIVA)***
Ans.

Impaired glucose tolerance (IGT): When a random or fasting blood glucose is suggestive but not diagnostic of DM, that means when the values are above the upper limits of normal but below the values of diagnostic of diabetes it is called impaired glucose tolerance (IGT).

Or,

When fasting glucose is less than 7 mmol, but during OGTT, 2 hours after the glucose load is 7.8 to 11.0 mmol, it is called IGT.

Diagnostic criteria: The WHO criteria for impaired glucose tolerance (IGT) -

	Impaired glucose tolerance
Fasting plasma glucose	6.1-6.9 mmol/L (110-125 mg/dl)
2 hrs after OGTT	7.8-11.0 mmol/L (140-199 mg/dl)

Advice to patients with IGT: The patient who has IGT are at increased risk of developing frank DM type 2 with time and also macrovascular complications are more (mainly cardiovascular). Lifestyle modification for type 2 DM and annual check-up for glucose are recommended for this patient. Cardiovascular risk factors should be treated aggressively.

(Ref: Lecture SSMC; Long Cases in Clinical Medicine/1st/610; Davidson's/23rd/726)

Q. How will you differentiate impaired glucose tolerance (IGT) from overt diabetes? (DU-04S)
Ans.

Differences between IGT and overt diabetes:

Traits	Impaired glucose tolerance (IGT)	Overt diabetes
1. Definition	Blood sugar is in between normal & DM	Blood glucose ≥ 11.1 mmol/L
2. Blood glucose	**Fasting:** 6.1-6.9 mmol/L (110-125 mg/dl) **2 hrs after OGTT:** 7.8-11.0 mmol/L (140-199 mg/dl)	**Fasting:** ≥ 7.0 mmol/L (≥126 mg/dl) **2 hrs after OGTT:** ≥ 11.1 mmol/L (≥ 200 mg/dl)
3. Urine sample	Corresponding urine sugar absent in all the samples	Corresponding urine sugar present when plasma glucose is above renal threshold

Q. An obese male of 58 years complaining of loss of weight and mild generalized weakness. Laboratory investigations reveal fasting blood sugar 6.6 mmol/L and random level 10.0 mmol/L. Serum lipid level is also raised. What is the diagnosis? How will you investigate the case? (DU-11Ju)

Ans.

Diagnosis: Impaired glucose tolerance (IGT).

Investigation: By OGTT.

Q. An obese female aged 45 years with glucosuria, found during routine medical check up. OGTT done and the results are as follows:

Time	*Plasma glucose*	*Urine glucose*
Fasting	5.4 mmol/l	(-)
1 hour	10.7 mmol/l	(+)
2 hours	9.9 mmol/l	(+)

How will you interpret this OGTT result? What is the underlying cause for this? (DU-08Ja)

Ans.

Interpretation of OGTT result: Impaired glucose tolerance (with renal glycosuria).

Underlying cause of renal glycosuria: *Please see the corresponding section before.*

Nice to Know:

Tests for blood glucose estimation:

i) Enzymatic method by using glucose oxidase
ii) Colorimeter
iii) Spectrophotometer
iv) Automated biochemistry analyzer
v) Test strips
vi) Chemical reduction method.

(Ref: Prof. Khaleque/193)

Glycosylated Haemoglobin (HbA_1C)

(Must be Asked in VIVA)

Q. What is the significance of HbA_1C? (CU-18Nv)

Q. Short note: Glycosylated haemoglobin (HbA_1C). (DU-21Ja,20Nv/M,16Ju, CMU-21Nv,20Ju, 16Ja,13Ju,11/10/09Ja)

Ans.

Glycosylated haemoglobin (HbA_1C): Glycosylated haemoglobin (HbA_1C) is the most widely used measure of long-term glycaemic control in diabetes mellitus. It is produced by the ***glycosylation of hemoglobin*** at a rate proportional to the glucose concentration.

*(**N.B:** Slow non-enzymatic covalent attachment of glucose to hemoglobin is called **glycosylation** of hemoglobin.)*

Normal value: 4.0 - 6.0% of total Hb.

Importance:

1. Glycosylated haemoglobin provides an accurate and objective measure of ***glycaemic control*** over a period of ***weeks to months***.

2. The measurement of HbA_1C level in the blood is a useful adjunct in ***monitoring*** the ***management*** of DM.
3. The rate of formation of HbA_1C is ***directly proportional*** to the ambient ***blood glucose concentration***. A rise of **1% in HbA_1C** corresponds to an approximate average increase of **2 mmol/L blood glucose.**
4. A large shift in blood glucose control is rapidly accompanied by a change in HbA_1C, detectable within **2 - 3 weeks.**
5. It also provides an **index** of risk for developing **diabetic complications.**

(Ref: Davidson's/23rd/726; Lecture SSMC; Prof. Khaleque/193)

Complications of Diabetes Mellitus

Q. What are the complications of diabetes mellitus? (DU-22M,21Ja,20Nv/M,19Nv,17/15Ja,13/12Ju, RMU-22Nv,18Ja,17Nv,11Ja,09Ju, BUP-22M, SU-20M, CU-19M)
Q. Mention the acute and chronic complications of diabetes mellitus. (CMU-22Nv)
Q. Short note: Complications of diabetes mellitus. (RU-15/14Ju)
Ans.

Complications of diabetes mellitus:

Acute complications:

1. Diabetes ketoacidosis
2. Hypoglycaemic coma
3. Hyperglycaemic hyperosmolar state (HHS)
4. Lactic acidosis

Chronic complications:

A) ***Microvascular / neuropathic:***

1. **Diabetic retinopathy**
   - Impaired vision
2. **Diabetic nephropathy**
   - Renal failure
3. **Diabetic neuropathy**
   - Sensory loss
   - Motor weakness
   - Pain
4. **Autonomic neuropathy**
   - Gastrointestinal problems (gastroparesis; altered bowel habit)
   - Postural hypotension
5. **Diabetic foot disease**
   - Ulceration
   - Arthropathy

B) ***Macrovascular:***

1. **Coronary circulation**
   - Myocardial ischaemia / infarction
2. **Cerebral circulation**
   - Transient ischaemic attack
   - Stroke
3. **Peripheral circulation**
   - Claudication
   - Ischemia (e.g. gangrene of the lower extremities).

(Ref: Davidson's/23rd/734,756; Robbin's/10th/1106,1107)

Q. What are the ketone bodies? (DU-11Ju,10Ja, RU-17/16Ja)
Q. Define ketonuria. How it is formed?
Ans.
Ketonuria: Acetoacetate, β-hydroxybutyrate, and acetone are collectively called ketone bodies or ketones. Excretion of more than a trace of these substances in the urine is called ketonuria.

Mechanism of formation of ketonuria: Glucose provides energy to our body. If intake is insufficient or metabolism defective due to lack of insulin as in untreated or uncontrolled diabetes, body obtains energy by breaking down fats & ketones. Ketones are toxic to brain and can cause coma found in diabetic ketoacidosis. In ketoacidosis, ketonuria is always present. Urine ketone test detect acetoacetate and acetone only.

(Ref: Lecture SSMC)

Q. How ketoacidosis develops in cases of uncontrolled diabetes mellitus? (DU-11Ju,10Ja,08Ju)
Q. Explain the mechanism of developing metabolic acidosis in diabetes mellitus. (DU-03M, RU-08Ju)
Q. Discuss in short about the pathogenesis of diabetic ketoacidosis. (DU-23Nv)
Q. Short note: Diabetic ketoacidosis. (DU-19M,18Ja)
Q. Short note on: Ketoacidosis. (DU-17Ja)
Ans.
Ketoacidosis / diabetic ketoacidosis: Over production of ketone bodies in long-standing uncontrolled or poorly controlled diabetes mellitus exceeds buffering capacity of blood. As a result, blood pH is decreased and acidosis is produced which is called ketoacidosis.

Mechanism of development of ketoacidosis in uncontrolled DM:

Diabetes mellitus
↓
↓Plasma insulin level
↓
↓Inhibitory effect of insulin on lipolysis
↓
↑Lipolysis
↓
↑Free fatty acid in plasma
↓
↑β-oxidation
↓
↑Acetyl CoA
↓
All the acetyl CoA cannot be hydrolyzed by TCA cycle in liver
↓
Excess acetyl CoA is converted to acetoacetic acid & 3-hydroxybutyric acids
↓
↑Ketone bodies in blood
↓
↑Excretion of ketone body (and glucose) in urine
↓
Dehydration
↓
↑Ketone bodies in decreased volume of plasma
↓
↑Plasma ketone body concentration
↓
Diabetic ketoacidosis

(Ref: Lippincott's/3rd/195)

Cardinal biochemical features: The cardinal biochemical features of diabetic ketoacidosis are-

1. Hyperglycaemia
2. Hyperketonaemia
3. Metabolic acidosis

(Ref: Davidson's/23rd/735)

Clinical features:

A. Symptoms:

1. Polyuria, thirst
2. Weight loss
3. Weakness
4. Nausea, vomiting
5. Leg cramps
6. Blurred vision
7. Abdominal pain.

B. Signs:

1. Dehydration
2. Hypotension
3. Cold extremities / peripheral cyanosis
4. Tachycardia
5. Air hunger (***Kussmaul breathing***)
6. Smell of acetone
7. Hypothermia
8. Confusion, drowsiness, coma (10%).

(Ref: Davidson's/23rd/735)

Management: The principle components of treatment are-

- The administration of short-acting (soluble) insulin
- Fluid replacement
- Potassium replacement
- The administration of antibiotics if infection is present.

(Ref: Davidson's/23rd/735)

Q. Mention the complications of diabetic ketoacidosis.

Ans.

Complications of diabetic ketoacidosis:

1. Cerebral edema
2. Acute respiratory distress syndrome
3. Thromboembolism
4. Disseminated intravascular coagulation (rare)
5. Acute circulatory failure.

(Ref: Davidson's/23rd/736)

Q. A 48 years old diabetic patient became unconscious following a chest infection. He did not take any anti-diabetic drugs. He also developed musty odour in breath. What is the diagnosis? What may be the likely findings in urine analysis?

Ans.

Diagnosis: Diabetes ketoacidosis.

{Note: Any form of stress, particularly that produced by infection, may precipitate severe ketoacidosis.}

(Ref: Davidson's/21st/809)

Likely findings in urine analysis:

- pH of urine: ↓
- Urinary glucose: ↑↑
- Urinary ketone body: ↑↑.

Q. A 26 years female, was brought to the hospital with a recent history of polyuria, nausea, vomiting, and abdominal pain. Blood parameters on admission was glucose 19 mmol/l, serum electrolytes-Na-120 meq/l, Cl-85 meq/l, K-2.5 meq/l, HCO_3^--10mmol/l. What is the likely diagnosis?

Ans.

Diagnosis: Diabetes ketoacidosis.

Gestational Diabetes Mellitus

Q. Define gestational diabetes mellitus. (DU-09Ja, RU-20Nv,18Ja)

Q. Short note: Gestational diabetes mellitus. (*Important for VIVA*)

Ans.

Gestational diabetes mellitus: Glucose metabolism changes during normal pregnancy. Gestational diabetes is defined as diabetes with first onset or recognition during pregnancy.

WHO suggests that all women meeting criteria for impaired glucose tolerance or diabetes after a 75 gm OGTT should be classified as having gestational diabetes.

Risk factors for gestational diabetes:

1. Obesity
2. Family history of type 2 diabetes
3. Previous glucose abnormality in pregnancy
4. Previous macrosomia

Complications of gestational diabetes:

1. Gestational diabetes is associated with an increased risk of later development of type 2 diabetes.
2. Maternal hyperglycemia is associated with increased fetal size (fetal macrosomia) & obstructed labour.

Diagnosis of gestational diabetes mellitus: The **European criteria** of diagnosis of gestational diabetes are:

- **Venous plasma glucose in the fasting state:** > 5.5 mmol/L (99 mg/dl)
- **2 hours after a glucose load:** > 9 mmol/L (162 mg/dl)

(Ref: Davidson's/23rd/752)

CHAPTER 04

SEMEN ANALYSIS

Q. What are the indications of semen analysis? (DU-23M,21Oct/M,19M,17/16/15/14/12Ja, CMU-23M,19Nv,11/08Ja, BUP-22Nv,21Nv/M, RMU-22/21M,20M,13/12Ju, SU-13Ja)
Q. Enumerate the medicolegal importance of semen analysis. (RU-15Ju)
Ans.

Indication of semen analysis: ***(Very Important for VIVA)***

1. Evaluation of male fertility
2. Paternity test
3. For artificial insemination
4. Follow up after vasectomy
5. In suspected rape case - for identification of the accused.

(Ref: Lecture SSMC, BSMMU Lab. Medicine & AFIP Clinical Pathology)

Q. How semen is collected for analysis? (DU-15Ja)
Ans.

Semen collection procedure:

1. **Preparation of the patient:**
   - Patient should be instructed to collect semen with a sexual abstinence of 3-5 days.
   - Should be obtained by masturbation (self stimulation) or collect at home during the act of intercourse (by coitus interruptus). Condom should be avoided, as it contains spermicidal agent.
   - Patient should evacuate his bladder before ejaculation.
2. **Collection of specimen and transport:**
   - Should be collected in a dry, clean plastic container provided by the laboratory.
   - Condom collection is unacceptable.
   - Patient's name, age, date and time of collection should be recorded.
   - Sample should be taken to the laboratory within 1 hour of collection and kept at body temperature.

(Ref: Lecture SSMC, BSMMU Lab. Medicine & AFIP Clinical Pathology)

Q. Write the advices before doing semen analysis. (CU-20Ju,16Ja, SU-13Ju)
Q. Mention the prerequisites before doing semen analysis. (CU-15Ja)
Ans.

Advices before doing semen analysis:

1. Semen should be collected after 3-5 days of sexual abstinence.
2. Should be obtained by masturbation or collect at home during the act of intercourse (by coitus interruptus). Condom should be avoided, as it contains spermicidal agent.
3. Patient should evacuate his bladder before ejaculation.
4. Should be collected in a dry, clean plastic container provided by the laboratory.
5. Condom collection is unacceptable.
6. Sample should be taken to laboratory within 1 hour of collection and kept at body temperature.

(Ref: Lecture SSMC, BSMMU Lab. Medicine & AFIP Clinical Pathology)

Q. Mention the normal findings of semen analysis. (DU-23/19M,17/16/15/14/12Ja, BUP-21Nv/M, RU-16Ju,14/11Ja, CU-10/09/07Ja)
Q. Write a normal semen analysis report. (CU-15/10Ja)
Q. What information we can get from semen analysis? (SU-13Ja)
Q. Write down the features examined in semen analysis? (CMU-22M,21Nv)
Q. Write important messages mentioned in semen analysis reporting. (DU-18Ja)
Q. Write the points to be noted in the macroscopic and microscopic evaluation of semen analysis. (CU-20Nv/M)
Q. Short note: Semen analysis. (DU-13Ja,10/09Ju,09/08/07Ja, SU-22Nv,21/20Nv,16Ja,11Ju, RU-15Ja, CU-09Ju)
Q. Short note: Normozoospermia. (RU-18M)

Ans.

Semen analysis: Semen analysis measures the quality and quantity of the fluid secreted during ejaculation. It evaluates both ***liquid portion*** called **semen** or **seminal fluid**, and microscopic ***moving cells*** called **sperm.**

It is often used to study the ***fertility status of a male.***

Basic semen analysis measures:

1. Semen volume
2. Sperm concentration
3. Sperm motility
4. Sperm morphology

Additional pH & fructose levels (absence of fructose or high pH may be associated with ejaculatory tract obstruction or seminal vesicle dysfunction) & WBC counts within semen can also be done.

Normal findings of semen analysis: ***(Please read this at least 10 times for VIVA)***

Traits	Normal level
Macroscopic examination	
1. Appearance	Opalescent / Opaque
2. Colour	Grayish white
3. Volume	2-5 ml / ejaculation
4. Viscosity	High
5. Consistency	Thick
6. Odour	Musty
7. pH range	7.2 – 7.8
Microscopic examination	
1. Sperm concentration	20-110 million / ml
2. Sperm motility	60-65% sperms are actively motile within 1 hour
3. Sperm morphology	>50% sperms are morphologically normal (normal head, body & tail)
4. Sperm viability	≥75% sperms are viable
5. Leucocytes	<1 million / ml
6. Liquefaction	Complete within 30 minutes

7. Sperm clumping	Absent
Biochemical test	
1. Fructose estimation	1.5 – 6.5 mg/dl

(Ref: Lecture SSMC, BSMMU Lab. Medicine & AFIP Clinical Pathology)

Nice to Know:

Semen volume:
- Normal ejaculated volume of semen is 2-5 ml.
- Low semen volume indicates retrograde ejaculation.
- High semen volume indicates long periods of abstinence or inflammation of the accessory glands.

Sperm concentration: Sperm conc. or density is defined as the number of sperm / ml in the total ejaculation. Most WHO laboratories recognize the value of 20 million/ml as a lower limit of normal.

Sperm motility: Sperm motility is defined as the percentage of progressively motile sperm in the ejaculate. Most WHO laboratories use a cut off of 50% motility as a lower limit of normal.

Sperm morphology: Greater than 30% normal are accepted by WHO.

(Ref: Lecture SSMC)

Q. Define oligospermia (DU-16/14Ja, CU-19M,10/07Ja) **& necrospermia.** (RU-03M)

Ans.

Sperm analysis terminology:

▪ **Normozoospermia**	All semen parameters are normal.
▪ **Oligozoospermia**	Reduced sperm number (<20 million sperm / ml of semen). ▪ **Mild to moderate:** 5-20 million / ml of semen. ▪ **Severe:** <5 million / ml of semen.
▪ **Asthenozoospermia**	Reduced sperm motility (<50% sperm has forward motility)
▪ **Teratozoospermia**	Increased abnormal forms of sperm (<30% are morphologically normal)
▪ **Azoospermia**	No sperm in semen
▪ **Aspermia**	Ejaculation failure (absence of semen)
▪ **Necrozoospermia**	All sperms are non-viable or dead
▪ **Polyzoospermia**	Sperm count is >350 million/ml

(Ref: Lecture SSMC, BSMMU Lab. Medicine & AFIP Clinical Pathology)

Q. How can you know male fertility status by examining semen? (RU-12Ju)

Ans.

Male fertility status by examining semen:

1. **Sperm count:**

Condition	Sperm count	Fertility status
▪ **Normozoospermia**	Sperm count is normal (≥ 20 million / ml)	Fertile
▪ **Oligozoospermia**	Reduced sperm count *(< 20 million / ml)* ▪ **Mild to moderate:** 5-20 million / ml of semen ▪ **Severe:** <5 million / ml of semen	Susceptible to infertility
▪ **Azoospermia**	No sperm in semen	Infertile
▪ **Necrozoospermia**	All sperms are non-viable or dead	Infertile
▪ **Polyzoospermia**	Sperm count is >350 million/ml	Susceptible to infertility

2. **Motility of sperm:** For normal fertility >50% spermatozoa must be motile.

3. **Morphology of sperm:** For normal fertility > 30% sperms must be morphologically normal *(normal head, body & tail).*

(Ref: Lecture SSMC)

Q. Short note: Oligospermia. (BUP-21Nv/M, SU-20M, RU-18Ja,09Ju)

Ans.

Oligospermia: Less than 20 million sperm/ml of semen.

Cause:

A. Idiopathic.

B. Pre-testicular cause:
- Hypogonadism due to any cause
- Drug, alcohol, smoking
- Heat
- Strenous riding of bicycle
- Tight fitting undergarments
- Diabetes mellitus
- Cancer treatment (radio/chemo therapy)
- Severe illness: Malignancy, liver failure, renal failure

C. Testicular cause:
- ↑ Age
- Genetic defect
- Chromosomal abnormality, e.g. Klinefelter's syndrome
- Cryptorchidism
- Orchitis
- Varicocele, hydrocele
- Trauma/surgery
- Neoplasm: Seminoma

D. Post-testicular cause:
- Infection: Prostatitis
- Obstruction in vas difference
- Obstruction in ejaculatory duct
- Absence of vas difference.

(Ref: Lecture SSMC, BSMMU Lab. Medicine & AFIP Clinical Pathology)

Q. What is azoospermia? (DU-18M, RMU-23M,19Nv) **What are the causes of azoospermia?** (DU-23/19M,18/17Ja, CMU-22Nv, BUP-16Ju)

Q. Mention 3 causes of azoospermia. (DU-15Ja)

Q. Short note: Azoospermia. (BUP-21Nv/M, SU-19Nv, RU-18M)

Ans.

Azoospermia: No sperm in semen. It is defined as the complete lack of sperm in the ejaculate. It occurs in 5% of infertile man.

Cause:

A. Idiopathic.

B. Pre-testicular cause:
- Hypogonadism due to any cause
- Drug, alcohol
- Diabetes mellitus
- Cancer treatment (radio/chemo therapy)
- Severe illness: Malignancy, liver failure, renal failure
- Haemochromatosis

- Sickle cell anemia

C. Testicular cause:

- 1°/2° testicular failure
- Genetic defect
- Chromosomal abnormality, e.g. Klinefelter's syndrome
- Cryptorchidism
- Orchitis
- Varicocele, hydrocele
- Trauma/surgery
- Sperm autoimmunity (anti-sperm Ab)

D. Post-testicular cause:

- Infection: Epididymitis, prostatitis
- Obstruction in vas difference
- Obstruction in ejaculatory duct
- Absence of vas difference
- Vasectomy.

(Ref: Lecture SSMC, BSMMU Lab. Medicine & AFIP Clinical Pathology)

Q. A male of 36 years presented with infertility. On semen analysis sperm was absent. (BUP-22M)

a) What will be your comment on semen analysis?

b) What may be the possible causes?

Ans.

a) **Comment:** Azoospermia.

b) **Possible causes:** *Please see above.*

Q. Short note: Oligoasthenozoospermia. (BUP-21N/M)

Ans.

Oligoasthenozoospermia: It is a sperm disorder that involves two disorders at the same time-

a) **Oligospermia:** Low sperm count.

b) **Asthenozoospermia:** Abnormal sperm motility with more than 60% of sperm being immotile or unable to move in a straight direction.

Causes:

a) In most cases causes are unknown / idiopathic.
b) Testicular diseases e.g. orchitis.
c) Some genetic disorders e.g. Klinefelter's syndrome, immotile cilia syndrome.
d) Immunologic.

Treatment: Treatment of reversible cause, if any.

Q. Mention the etiological factors of male infertility. (RU-10Ja)

Ans.

Etiological factors of male infertility: ***(Very Important for VIVA)***

A. Failure of spermatogenesis:

- Incomplete development of testis / undescended testis
- Absence of testis
- Orchitis (due to Mumps / influenza / Chlamydia)
- Cryptorchidism

- Chromosomal abnormality: Klinefelter's syndrome
- Damage of testis (due to radiation, trauma or heat)
- Diseases of testis (TB, syphilis, seminoma)
- Varicocele
- Drugs – Nicotine, Sulfonamide, Antihistamine, cytotoxic drugs, Alcohol, pesticides etc.
- Anti-sperm antibody
- Endocrine disease:
  - Hypothalamic pituitary dysfunction due to trauma, radiation, tumour and surgery
  - Hyperprolactaemia
  - Thyroid disorder (thyrotoxicosis/hyperthyroidism)
  - Adrenal hyperplasia
- DNA damage by reactive oxygen species, fever and high testicular temperature
- General factors: DM, smoking

B. Failure of transport of semen due to bilateral obstruction of epididymis, vas deferens or ejaculatory duct.

C. Failure of deposit sperm in vagina, e.g. impotency, retrograde ejaculation, premature ejaculation.

D. Errors of seminal fluid: Low volume, physiochemical abnormality of semen (azoospermia, oligospermia, teratospermia, hypospermia etc.)

(Ref: Lecture SSMC, BSMMU Lab. Medicine & AFIP Clinical Pathology)

Q. Define pseudocyesis. (RMU-23M,19Nv)

Ans.

Pseudocyesis (false pregnancy): Pseudocyesis is a syndrome when a woman shows all the symptoms of being pregnant except for the presence of a fetus.

Their belly grows like a pregnant woman, and they can even go into false labour.

Q. How will you proceed to diagnose a case of male (RU-15/13Ju) **and female infertility?** (RU-13Ju)

Q. Short note: Infertility test.

Ans.

Infertility test: Infertility test are meant to establish the reason why a couple is not able to conceive naturally. Overall, 20-30% of the cases of infertility are due to a problem with the male partner.

Diagnosis of male infertility:

1. **Medical, sexual and social history**
2. **General physical examination** (including an examination of genitals)
3. **Specific fertility tests:**
   - Semen analysis
     - Physical, chemical and microscopic test
     - Immunological assay
     - Anti-sperm antibody test
     - Sperm function test
     - Post ejaculatory urine analysis
   - Hormone testing (testosterone and other male hormones)
   - Transrectal and scrotal ultrasound
   - Genetic testing

Diagnosis of female infertility:

1. **Medical, sexual and social history**
2. **General physical examination** (including a regular gynaecological examination)
3. **Specific fertility tests:**

- **Hormone assay** (LH, FSH, estradiol, progesterone, prolactin, thyroid & pituitary hormone)
- **Hysterosalpingography** (a special X-ray test to locate blockage or other problems in the uterus and fallopian tube)
- **Ovulation testing** *(blood test to measure hormone levels to determine whether the patient is ovulating or not)*
- **Ovarian reserve test** *(this test helps to determine the quality and quantity of the eggs available for ovulation)*
- **Diagnostic laparoscopy** *(this can identify endometriosis, scarring, blockages or irregularities of the fallopian tubes, and problems with the ovaries and uterus)*
- **Imaging tests (e.g. pelvic ultrasound, hysterosonography, hysteroscopy etc.)**
- **Endometrial biopsy** *(to verify ovulation and inspect the lining of the uterus)*
- **Pap's smear**
- **Genetic testing** (to determine whether there is a genetic defect causing infertility).

(Ref: Lecture SSMC, BSMMU Lab. Medicine & AFIP Clinical Pathology)

Q. What are the common hormones done in male and female to evaluate infertility? (DU-13Ju)

Ans.

Common hormones done in male to evaluate infertility:

1. Testosterone
2. Thyroid hormone
3. Prolactin

Common hormones done in female to evaluate infertility:

1. Progesterone
2. Follicle stimulating hormone (FSH) *(on day 3 of the menstrual cycle)*
3. Luteinizing hormone (LH)
4. Thyroid hormone
5. Prolactin
6. Testosterone
7. Anti-Mullerian hormone.

CHAPTER 05

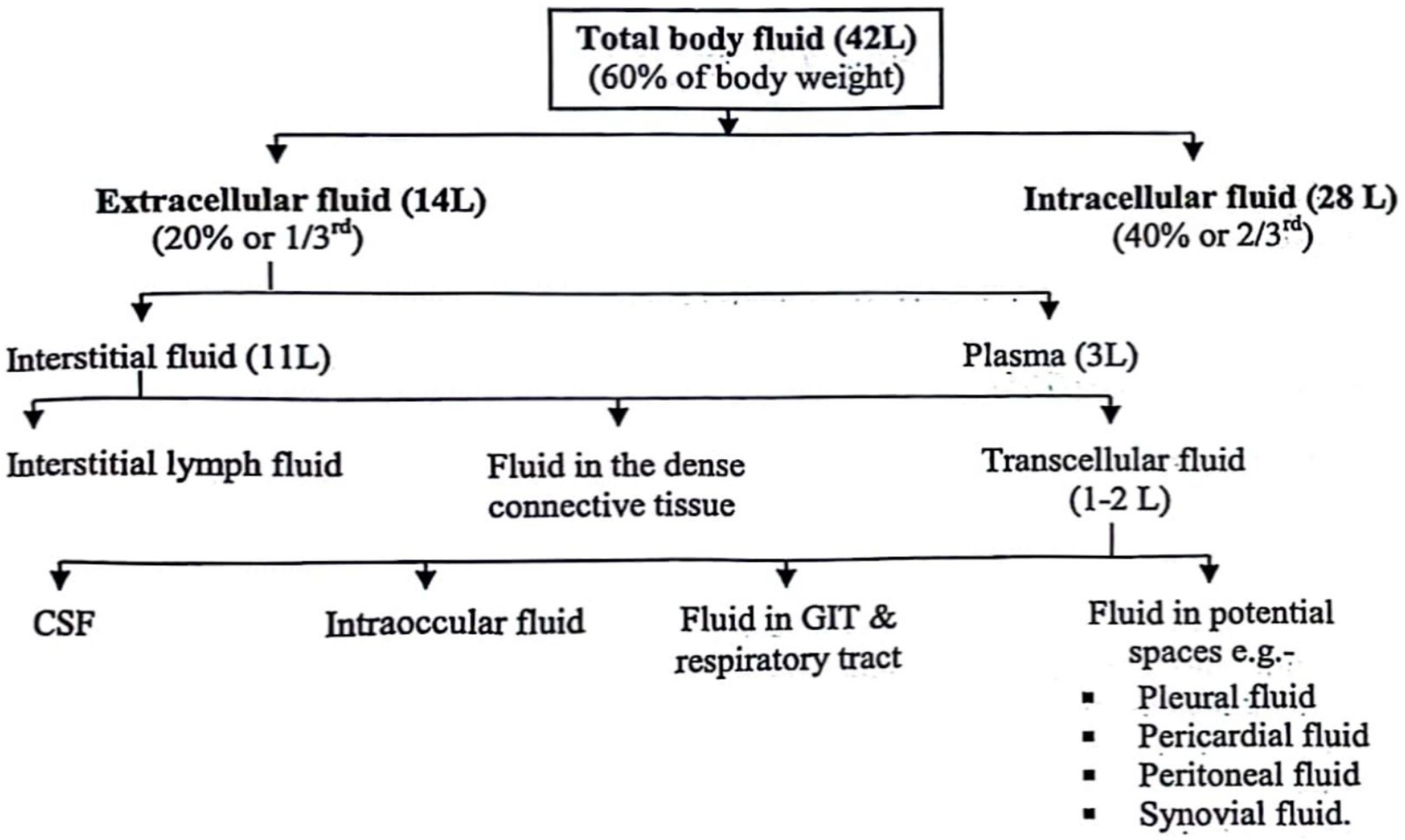
BODY FLUIDS

Q. What are the body fluids? (DU-09Ja)

Ans.

Body fluid: The fluid present in different compartments of the body is called body fluid.

Fluid compartments of the body:



(Ref: Guyton/11th/292; Lecture SSMC)

Q. Name the important body fluids commonly send to the laboratory for examination. (DU-21Oct/M,12Ja, RU-17/10Ja)
Q. Name the body fluids usually examined in our clinical practice. (DU-16/13/10Ju)
Q. Name the body fluids of clinical significance. (RU-12Ja)
Ans.
Commonly examined body fluids:

1. Plasma
2. CSF
3. Pleural fluid
4. Peritoneal fluid
5. Synovial fluid
6. Pericardial fluid
7. Hydrocele fluid
8. Amniotic fluid
9. Saliva and gastric juice
10. Semen.

(Ref: Lecture SSMC)

CSF Examination & Meningitis

Q. Name the indications of CSF examination. (DU-22M,19Nv,18M,18/07Ja, SMU-23M,22Nv/M,21/20Nv,19/18M,15Ju,14Ja,11Ju/Ja,10/09Ju, CMU-23M, RMU-23/22M,18M/Ja,17Ja,15/13/12/11/10/09Ju, 07Ja)
Q. Name 5 important indications of CSF study. (DU-09Ju, CU-17M)
Q. Write the indication / significance of routine CSF examination. (SU-04Ja)
Q. Short note: Indication of CSF examination. (RU-08Ju)
Ans.
Indication of CSF examination: ***(Very Important for VIVA)***

1. **Infections:**
   - ***Meningitis***
   - ***Encephalitis***
2. ***Cerebral abscess***
3. ***Sub-arachnoid hemorrhage*** (If CT-scan is -ve or unavailable)
4. **Inflammatory conditions**
   - ***Gullain-Barre syndrome (GBS)***
   - ***Neurosyphilis***
   - Acute poliomyelitis
   - Multiple sclerosis
   - Sarcoidosis
   - Acute polynuritis
   - SLE
5. **Infiltrative conditions/ neurological malignancies**
   - Carcinomatous meningitis
   - Lymphoma
   - Leukaemia
6. **To confirm raised intracranial pressure** (when CT scan excludes danger of brain stem herniation)
   - Benign intracranial hypertension (BIH)
   - Cerebral venous thrombosis.

(Ref: Lecture SSMC; Davidson's/23rd/1077)

Q. What is lumber puncture?

Ans.

Lumbar puncture: It is the technique used to obtain both a CSF sample and an indirect measure of intracranial pressure.

(Ref: Davidson's/23rd/1077)

Q. Write the indications of lumber puncture. (RU-08Ja)

Ans.

Indication of lumbar puncture:

A. Diagnostic:

1. **Infections**
   - Meningitis
   - Encephalitis
2. **Cerebral abscess**
3. **Sub-arachnoid hemorrhage** (If CT scan is -ve or unavailable)
4. **Inflammatory conditions**
   - Acute poliomyelitis
   - Multiple sclerosis
   - Sarcoidosis
   - Acute polynuritis
   - SLE
   - Neurosyphilis
5. **Primary or secondary metastatic malignancies**
   - Carcinomatous meningitis
   - Lymphoma
   - Leukaemia
6. **To confirm raised intracranial pressure (when CT scan excludes danger of brain stem herniation)**
   - Benign intracranial hypertension (BIH)
   - Cerebral venous thrombosis

B. Therapeutic:

1. **Administration of the drugs**
   - Antibiotics (meningitis)
   - Antimitotics (oncology)
2. **Instillation of contrast media or isotopes**
   - Myelography
   - Cisterography
3. **Spinal anesthesia.**

(Ref: Lecture SSMC; Davidson's/23rd/1077)

Q. How will you differentiate subarachnoid haemorrhage from traumatic haemorrhage? ***(Very Important for VIVA)***

Ans.

Differentiation between subarachnoid haemorrhage (SAH) from traumatic haemorrhage:

- In SAH → there is yellow supernatant plus blood is uniformly mixed.
- In traumatic haemorrhage → supernatant is clear plus blood is not uniformly mixed.

Q. Write down the contraindications of lumber puncture. ***(Very Important for VIVA)***

Ans.

Contraindications of lumber puncture:

1. Local tissue suppuration
2. Raised intracranial pressure
3. Suspected intracranial mass lesions
4. Patient is on aspirin, heparin, warfarin therapy
5. Depressed level of consciousness
6. Bleeding disorder
7. Lack of cooperation.

(Ref: Davidson's/23rd/1077; Lecture SSMC; BSMMU Lab. Medicine; AFIP Clinical Pathology)

Q. What are the complications of lumbar puncture?

Ans.

Complications of lumbar puncture:

- Infection
- Brain stem herniation
- Post lumber puncture headache
- Injury to intervertebral disk
- Bleeding due to injury to vertebral plexus
- CSF leakage
- Local pain
- Shock
- Transient ischemic attack (TIA)
- Vaso-vagal attack.

(Ref: Davidson's/23rd/1077; Lecture SSMC)

Q. What are the tests done in CSF examination? (DU-04S)

Ans.

Tests done in CSF examination:

1. **Physical examination:**
   - Quantity or volume
   - Colour
   - Appearance
   - Pressure
   - Specific gravity
   - Presence of blood
   - Clot formation (CSF is normally clear and colorless)
2. **Cell count:** Mainly lymphocytes (normally 0-5 lymphocytes / mm^3)
3. **Chemical examination:** Protein, glucose & chloride levels
4. **Bacteriological examination:**
   - **Staining:** Gram staining for ordinary bacteria & ZN staining for tubercle bacilli
   - **Culture & sensitivity:** Chocolate agar media for ordinary bacteria & Lowenstein-Jensen media for M. *tuberculosis*
5. **Microbiological examination:** PCR for herpes simplex or TB
6. **Serological examination:**
   - VDRL for syphilis
   - Complement fixation test (CFT)
   - Latex agglutination test
7. **Cytological examination:** To detect malignant cells.

(Ref: Prof. Khaleque/199; Davidson's/21st/1147)

(***N.B***: CSF examination must be done **within 30-60 minutes** after CSF collection.)

Q. Name the procedure / steps of CSF collection. (CU-07Ja, RU-03M)
Q. How CSF is collected? (CU-14/11Ja)
Ans.
Procedure of CSF collection:
Collection site:

1. Lumbar puncture (usually between L_3 and L_4)
2. Sub-occipital (cisternal) puncture
3. Lateral cervical puncture
4. Through ventricular canulas or shunts

Steps of CSF collection:

1. Explain the procedure to the patient including potential complications.
2. CSF must be collected as aseptically as practicable.
3. The fluid is collected from the sub-arachnoid space of spinal cord by a sterile lumbar puncture needle which is inserted into the L_3 and L_4 intervertebral space under local anesthesia.
4. CSF is also collected by cysternal puncture (sub-occipital puncture).
5. Sterile plastic tube should be used to collect CSF.
6. Total 6 - 10 ml may be collected.
7. Total 4 samples are usually collected in 4 sterile tubes and immediately labeled with patient's name:
   - Tube 1: For biochemical & immunological test.
   - Tube 2: For microbiological test.
   - Tube 3: Cell count and differentiation.
   - Tube 4: Cytology, if malignancy suspected.

(Ref: Prof. Khaleque/285; Lecture SSMC; DMC; BSMMU Lab. Medicine; AFIP Clinical Pathology)

Q. Write down the physical and biochemical characteristics of normal CSF. (DU-15Ju)
Q. Write down the biochemical and cytological findings of normal CSF. (SU-09Ja)
Q. Give the normal values of CSF cell count, total protein and glucose.
Q. Write down the normal findings of CSF. (DU-14Ju)
Ans. ***(Must be asked in VIVA)***
Normal findings of CSF:
Physical:

- **Pressure:** 50-250 mm of water.
- **Colour:** Clear.

Cytological:

- **Cell type:** Lymphocyte (mainly).
- **Cell count:** 0 - 4 / mm^3 of CSF.

Biochemical:

- **pH:** 7.3 - 7.7 (alkaline).
- **Glucose:** >50-60% of blood level (50 - 70 mg / dl).
- **Protein:** 15 - 45 mg / dl (<0.45 g/L).
- **Chloride:** 710 - 750 mg / dl.

Microbiological: Sterile.

(Ref: Davidson's/23rd/1078; Prof. Khaleque/199)

Q. State the clinical significance of low CSF sugar.
Ans.
Clinical significance of low CSF sugar:

1. It is useful to differentiate pyogenic meningitis from other meningitis

2. In pyogenic meningitis, CSF sugar is very low or absent
3. It indicates that the pyogenic organisms utilize sugar as food.

Q. What are the causes of high protein level in CSF? (SU-15Ja, SU-10Ja)

Ans.

Causes of high protein level in CSF: Any inflammatory condition, such as-

1. Pyogenic meningitis
2. Tubercular meningitis
3. Viral meningitis
4. Guillain Barre syndrome (GBS).

Q. What is meningitis? (DU-21Ja,20Nv/M,08Ja, BUP-22Nv, CU-11Ju,03Ja)
Q. Classify meningitis. (DU-21Ja,20Nv/M, SU-09/03Ja)
Q. What are the causes of meningitis? (SU-13Ju, CU-09Ju)
Q. What are the causes of neonatal meningitis? (DU-23Nv)
Q. Write down the bacterial causes of meningitis. (BUP-22Nv)

Ans.

Meningitis: Inflammation of the meninges is called meningitis.

Causes of meningitis:

Infective:

A. *Bacterial (mainly):*

1st 6 weeks (neonatal meningitis):

- *E. coli* (mainly)
- *Proteus*
- Group B streptococci
- *Listeria monocytogenes*

6 weeks to 6 years (pre-school child):

- *Haemophilus influenzae*
- *Neisseria meningitidis*
- *Streptococcus pneumoniae*
- *Mycobacterium tuberculosis*

Older child and adult:

- *Neisseria meningitidis*
- *Streptococcus pneumoniae*
- *Listeria monocytogenes*
- *Mycobacterium tuberculosis*
- *Staphylococcus aureus*
- *H. influenzae.*

B. *Viral:*

1. Enteroviruses (echo, Coxsackie, polio)
2. Mumps virus
3. Influenza virus
4. Herpes simplex virus
5. Varicella zoster-virus
6. Epstein-Barr virus
7. HIV virus

C. *Protozoa & parasites:*

1. Cysticerci
2. Amoeba

D. ***Fungal:***
1. *Cryptococcus neoformans (mainly)*
2. *Candida*
3. *Histoplasma*
4. *Blastomyces*
5. *Coccidioides*
6. *Sporothrix.*

Non-infective ('sterile'):

A. Malignant disease
- Breast cancer
- Bronchial cancer
- Leukaemia
- Lymphoma

B. Inflammatory disease (may be recurrent)
- Sarcoidosis
- Systemic lupus erythematosus
- Behcet's disease.

(Ref: Davidson's/23rd/1118; Lecture SSMC)

Q. Tabulate the laboratory findings of bacterial, viral and tubercular meningitis. (DU-08Ja, RU-09Ju)
Q. Give differences between CSF findings of pyogenic, tubercular and viral meningitis. (DU-22M)
Q. Mention the morphological differences of CSF in three types of meningitis. (DU-10Ju)
Q. Describe the CSF findings in different types of meningitis. (SMU-23M,22Nv/M,21/20Nv,19M)
Q. Compare the laboratory findings of pyogenic meningitis with viral meningitis in a tabulated form. (DU-18M,09Ja, RU-12Ja)
Q. How will you differentiate pyogenic (bacterial) and tubercular meningitis by examining CSF? (DU-23Nv,18/12Ja,09Ju, BUP-22M, SU-11Ju, RU-17Ja,10Ju, CU-11Ju,07Ja)
Q. Give the laboratory diagnosis of pyogenic/bacterial meningitis. (DU-14Ju, CU-17M,14Ja,11Ju, RU-16Ju,08Ja, SU-15Ja,10/09Ju)
Q. Write the findings of CSF study in pyogenic meningitis. (DU-21Ja,20Nv/M,16Ju, RMU-23/20/19M, BUP-22Nv, CU-16Ja)
Q. Write the CSF findings of tubercular & fungal meningitis. (SU-18M)
Q. State the CSF findings of tubercular meningitis. (DU-21Ja,20Nv/M, RMU-22Nv,15/13/11Ju,08Ja, CMU-21Nv,19M,18Nv,15Ju,14Ja,11/10Ju, SU-15Ju,14Ja,13Ju,11/08Ja)
Q. State the important CSF findings in viral meningitis. (DU-16/14Ju, BUP-22Nv, SU-10Ja)
Q. Mention the differences between pyogenic and tubercular meningitis. (DU-19Nv,13Ju,07Ja, RU-18Ja,14Ju, 07Ja)
Q. Mention the differences between tubercular and viral meningitis. (DU-15Ju,07Ja, CU-11Ja, RU 07Ja)
Mention the investigations needed to confirm such cases. (DU-19Nv)
Q. Write the causes of high protein level in CSF. Write the CSF finding of viral meningitis. (SU-10Ja)
Q. Short note on: Bacterial/pyogenic meningitis. (DU-10Ja, BUP-21Nv/M, CU-10Ja)

Ans.

CSF changes in different types of meningitis: ***(Please read this at least 10 times for VIVA)***

Traits	Normal	Pyogenic / Bacterial meningitis	Viral meningitis	Tubercular meningitis	Fungal meningitis
Physical					
Pressure	50-250 mm H_2O	Normal/ increased	Normal	Normal/ increased	Normal/ increased

Colour	Clear	Cloudy or hazy *(Clot may form)*	Clear *(No clot)*	Clear/cloudy *(Cob web or spider web clot formation)*	Clear
Cytological					
Cell count /mm^3	0-4 lymphocytes	1000-5000 ***neutrophils***	10-2000 ***lymphocytes***	50-5000 ***lymphocytes***	50-500 ***lymphocytes***
Biochemical					
Glucose	> 50-60% of blood levels	Decreased	Normal	Decreased	Decreased
Protein	150-450 mg/L (< 0.45 g/L)	Increased	Normal/ increased	Increased	Increased
Chloride	710-750 mg/dl	Normal/slightly decreased	Normal	Decreased/ Normal	Decreased/ Normal
Microbiological					
Staining		Organism found on ***Gram stain***	Usually not done	Acid fast bacilli on ***Ziehl-Nielson /Auramine stain***	***Gram stain (+/-) or India ink (+)***
Culture	Sterile	Organisms on ***blood agar/ Mac. Conkey's/ Chocolate agar*** media	Usually not done	Organisms on ***Lowenstein-Jensen (LJ)/ Middlebrook media***	Positive fungal culture on ***Sabouraud dextrose agar (SDA)*** media

(Ref: Davidson's/23rd/1078,1118; Lecture DMC)

Q. What is pleocytosis? (DU-10Ju)

Ans.

Pteocytosis: Pleocytosis is a term used to describe an increased cell count (Gk. *pleion* = more), usually referring to an increase in white blood cell (WBC) count in a bodily fluid, such as cerebrospinal fluid (CSF). It is often defined specifically as an increased WBC count in CSF.

Importance: It is indicative of an inflammatory, infectious, or malignant condition.

Q. A male of 25 years presented with high fever and neck rigidity. Haematological examination shows total WBC count is 18,000/cumm of blood. What is your clinical diagnosis? What investigations you will do to confirm the diagnosis? (DU-23M)

Q. A male of 35 years presented to you with high fever and neck rigidity for last 3 days. What is the probable diagnosis? How will you confirm the diagnosis with interpretation? (DU-22Nv)

Q. A boy of 7 years presented with short history of high fever and neck rigidity. What is your provisional diagnosis? How will you confirm the diagnosis? (RMU-21M)

Q. A male of 35 years complains of high fever and stiffness of neck for 3 days. On examination kernig's sign is positive. What is the probable diagnosis? How will you confirm the diagnosis? (DU-21Oct/M)

Ans.

Clinical diagnosis: Meningitis (probably pyogenic).

Confirmatory investigation: CSF analysis *(Please write from above).*

Q. A boy of 12 years complains of high fever, neck pain and restricted movement. His total count of WBC is 25000/cumm. What is the possible diagnosis? What are the possible etiologies? (DU-18Ja)

Ans.

Possible diagnosis: Meningitis (probably pyogenic).

Possible etiologies of pyogenic meningitis of a 12 years old boy:

- *Neisseria meningitidis*
- *Streptococcus pneumoniae*
- *Listeria monocytogenes*
- *Mycobacterium tuberculosis*
- *Staphylococcus aureus*
- *H. influenzae.*

Q. A child of 5 years presented with sudden attack of high grade intermittent fever with neck rigidity and purpuric rash throughout the whole body. What is your provisional diagnosis? Give the expected CSF findings in this case. (DU-17M,07Ju)

Ans.

Diagnosis: Meningococcal meningitis.

*{**Note:** The child has features of meningitis. In case of Meningococcal infection there is purpuric rash in the body.}*

CSF findings:

Physical:

- Pressure – increased
- Colour – cloudy or hazy

Cytology:

- Cell count – 1000-5000/mm^3
- Predominantly neutrophil

Biochemical:

- Protein – normal / elevated
- Glucose – decreased

Gram stain: Gram positive diplococci

Culture in blood agar media: Growth found.

Q. A male of 25 years came with high fever and neck pain with restricted movement. His total count of WBC is 18000/cumm of blood. What is your clinical diagnosis? What investigations you will do to further confirm the diagnosis? (DU-17Ja)

Ans.

Clinical diagnosis: Meningitis (probably pyogenic).

Confirmatory investigation: CSF analysis *(Please write from above).*

Q. A girl of 12 years presented with high fever and neck rigidity. What is your diagnosis? What will be the biochemical findings of CSF? (DU-16Ja)

Q. A boy of 12 years presented with high fever, neck pain and neck rigidity. CSF analysis shows increased leukocyte count. What is your diagnosis? What will be the biochemical findings of CSF? (DU-15Ja)

Ans.

Diagnosis: Meningitis (probably pyogenic).

Biochemical findings of CSF: *Please write from above.*

Q. A child aged 6 years was brought to the hospital with headache, fever, drowsiness, and neck stiffness. He had been suffering from recurrent otitis media. What is the likely diagnosis? How will you confirm in the laboratory? Give positive findings.

Ans.

Diagnosis: Meningitis (Most probably due to *H. influenzae* or *S. pneumoniae*).

*{**Note:** The child has features of meningitis. In case of H. influenzae* and *S. pneumoniae there may be otitis media}*

Laboratory investigations:

Physical:

- Pressure – increased
- Colour – cloudy or hazy

Cytology:

- Cell count – 1000-5000/mm^3
- Predominantly neutrophil

Biochemical:

- Protein – normal / elevated
- Glucose – decreased

Gram stain: Gram positive diolococci (*S. pneumoniae*) or gram negative bacilli (*H. influenzae*)

Culture: Blood agar media for *S. pneumoniae* and Chocolate agar media for *H. influenzae.*

Q. A 6 years malnourished child is admitted to hospital with manifestations of low grade fever for 15 days, gradual loss of consciousness for last 3-4 days, neck rigidity. What is the most probable diagnosis? What laboratory tests are to be done?

Ans.

Probable diagnosis: Meningitis, probably tubercular.

*{**Note:** The child has features of meningitis. Low grade fever for 15 days, malnourished child – all these go in the favor of TB)*

Laboratory tests to be done:

1. **Lumber puncture & CSF study:**
   - Colour- Clear / cloudy
   - Cell count - 50 – 5000 / mm^3; mainly lymphocytes
   - Glucose - low, typically < 40 mg/dL
   - Protein – elevated
   - AFB staining - may be positive
   - Culture in Lowenstein Zensen media - growth found
   - ADA (Adenosine deaminase) – elevated
2. **Complete Blood Count:** low Hb%, ESR may be high
3. **Chest X-ray**
4. **Tuberculin test**
5. **Gastric aspirates for AFB & culture.**

arif's special for VIVA on CSF Examination & Meningitis

Q. A patient with pyogenic meningitis comes to you, but CSF finding shows that CSF glucose is high. How it can be possible?

Ans.

The patients has ***uncontrolled DM***.

We know,

CSF glucose = 60% of blood glucose level

If blood glucose level = 100 mg /dl

Then, normal CSF = 60 mg/dl

If the patient has > 200 mg/dl blood glucose level

Then his normal CSF level will be > 120 mg/dl.

So, although this patient has pyogenic meningitis, CSF glucose will be higher than normal.

Q. Mention the hallmark of meningitis caused by *Neisseria*.

Ans.

Meningococcal skin rash.

Q. Mention two important physical sign in meningitis.

Ans.

1. Neck rigidity
2. Kernig's sign (extension at the knee with the hip joint flexed causes spasm in the hamstring muscles)
3. Brudzinski's sign (passive flexion of the neck causes flexion of the hips and knees).

(Ref: Davidson's/23rd/1019)

Q. Why CSF looks cloudy or turbid?

Ans.

Due to excess amount of protein.

Q. Why protein is increased in all types of meningitis?

Ans.

Because it is an inflammation and in every inflammation, there is exudate formation, which contains much more protein.

Q. Why CSF sugar is markedly reduced in pyogenic meningitis? (DU-23Nv)

Ans.

Because every pyogenic bacteria consumes glucose as their food and energy.

Q. Why glucose is normal in viral meningitis?

Ans.

Because virus dose not consume glucose.

Q. What do you mean by asceptic meningitis?

Ans.

It usually refers to viral meningitis.

Q. Name one special test for tubercular meningitis.

Ans.

ADA test.

Q. Mention the commonest cause of pyogenic meningitis.
Ans.
Neisseria meningitides.

Q. Mention the commonest cause of viral meningitis.
Ans.
- Echo virus
- Coxsackie virus.

Pleural Fluid Study

The fluid which is present in pleural cavity is called **pleural fluid.** Normal amount: 1-10 ml. Abnormal accumulation of fluid more than this level called **pleural effusion.**

Q. Mention the significance of pleural fluid study. (CU-08Ju)
Ans.
Significance of pleural fluid study: By studying pleural fluid, we can detect the following diseases-

Exudative pleural fluid: (High protein content)
1) Pulmonary tuberculosis
2) Pneumonia (para-pneumonic effusion)
3) Bronchial carcinoma
4) Pulmonary infarction
5) Collagen disease (SLE, rheumatoid arthritis)
6) Lymphoma

Transudative pleural fluid: (Low protein content)
1) Congestive cardiac failure
2) Nephrotic syndrome
3) Cirrhosis of liver
4) Malnutrition
5) Hypothyroidism
6) Meig's syndrome (ovarian fibroma, ascites and right sided pleural effusion)
7) Acute rheumatic fever.

The cause of majority of the pleural effusions can usually be identified through a thorough history, clinical examination and relevant investigations.

(Ref: Davidson's/23rd/563)

Q. Write down the possible findings in a patient with tubercular pleural effusion. (CU-20Nv/M,18/17M,16/08Ju)
Q. State the biochemical findings of tubercular pleural effusion. (CU-12Ju)
Ans.
Findings in tubercular pleural effusion:

1. **Appearance of fluid:** Serous, usually amber-coloured.
2. **Type of fluid:** Exudate.
3. **Predominant cells in fluid:** Lymphocytes (occasionally polymorphs).
4. **Biochemical findings:**
   - ***Protein:*** Increased
   - ***Sugar:*** Decreased
   - ***Adenosine deaminase (ADA):*** Increased (>40 U/L)
5. **Other diagnostic features:**

- Positive tuberculin test
- Isolation of M. *tuberculosis* from pleural fluid (20%)
- Positive pleural biopsy (80%).

(Ref: Davidson's/21st/659)

Q. State the findings of pleural fluid study in malignant pleural effusion. (CU-20/13Ju)

Ans.

Findings of pleural fluid study in malignant pleural effusion:

1. **Appearance of fluid:** Haemorrhagic.
2. **Type of fluid:** Exudate.
3. **Predominant cells in fluid:** Lymphocytes.
4. **Biochemical findings:**
   - ***Protein:*** Increased
   - ***Sugar:*** Normal
   - ***Adenosine deaminase (ADA):*** Normal
5. **Other diagnostic features:**
   - No organism is isolated in Gram stain, AFB stain or culture in Lowenstein-Jensen media.
   - Positive pleural biopsy
   - Malignant cells are found in Papanicolau stain.

Ascitic Fluid Study

Q. Short note: Ascitic fluid study. (CMU-22M,13Ja,12Ju)

Ans.

Ascitic fluid study: Ascitic fluid should undergo gross inspection as well as laboratory analysis. Routine laboratory test include:

- Differential cell count
- Albumin assay
- Cultures.

Inspection: Ascitic fluid is typically ***translucent*** and ***yellow***. Fluid of other colour or consistency may reflect specific underlying disease processes-

Disease	Ascitic fluid appearance
Cirrhosis	Straw-coloured, or bile stained
Neoplasm	Straw-coloured, hemorrhagic, mucinous, or chylous
Tuberculous peritonitis	Clear, turbid, hemorrhagic, or chylous
Pyogenic peritonitis	Turbid, or purulent
Congestive heart failure	Straw-coloured
Nephrosis	Straw-coloured, or chylous
Pancreatic ascites (pancreatitis, pseudocyst)	Turbid, hemorrhagic, or chylous

(Ref: School of Medicine, Queen's university)

Cell count: Several millileters of ascitic fluid is sufficient to obtain a differential cell count.

Albumin:

Exudative ascetic fluid (High protein content)	Transudative ascetic fluid (Low protein content)
▪ Peritoneal tuberculosis ▪ Pancreatitis ▪ Malignancy involving peritoneum	▪ Heart failure ▪ Cirrhosis of liver ▪ Nephrotic syndrome

▪ Budd-Chiary syndrome ▪ Portal vein thrombosis	▪ Malnutrition leads to hypo-proteinaemia

Culture and Gram stain: The most valuable method for determining the presence of infection is culture.

Miscellaneous: Optional tests include measurement of ***total protein***, ***glucose***, ***lactate dehydrogenase***, and ***amylase***. These will be beneficial in selected circumstances and need not be obtained on a routine basis.

Q. Write down the positive findings of exudative ascitic fluid. (CMU-21M)

Ans.

Positive findings of exudative ascitic fluid:

1. **Protein:** >25 gm/L
2. **Triglyceride:** Elevated
3. **Glucose:** Decreased
4. **Amylase:** Increased
5. **Alkaline phosphatase:** Increased.

CHAPTER 06

ELECTROLYTE AND ACID-BASE BALANCE

Electrolytes

Q. What are the electrolytes that are done to evaluate a patient? Give their normal levels. (DU-16Ja)
Q. Give the normal level of serum electrolytes. (DU-15Ja) **Mention the clinical importance of serum electrolytes.** (SU-19Nv,17M)
Q. Write down the components of electrolytes with their normal values. (CMU-21M)
Q. Give the normal serum levels of Na^+, K^+, Cl^- HCO_3^- and Ca^{2+}. (DU-05Ja)
Q. Short note: Serum electrolytes. (CU-15Ja)
Ans.
Serum electrolytes: Serum electrolytes are the salts and metallic components that are dissolved within the blood serum (serum is the liquid portion of blood).

Electrolytes carry an electrical charge, either negative or positive. The negatively charged electrolytes are balanced by the positively charged electrolytes.

Normal level of serum electrolytes:

Electrolytes	Reference range (mmol/L or meq/L)
Na^+	135 - 145
K^+	3.6 - 5.1
Cl^-	95 - 107
HCO_3^-	21 - 29
Ca^{2+}	2.1 - 2.6 (9-11 mg/dl)

(Ref: Davidson's/21st/1294,1296)

Importance of serum electrolytes: Electrolytes are involved in most of the body's daily functions. For example, electrolytes are required for:

- Proper nerve conduction
- Heart and skeletal muscle contraction
- Maintenance of proper hydration status

- Maintenance of proper blood pH.

Hypokalaemia

Q. Mention the causes (CU-18Nv)**, clinical features and investigations of hypokalaemia.**
Q. What are the complications of hypokalaemia? (CMU-21M)
Q. Short note on: Hypokalaemia.
Ans.
Hypokalaemia: Decreased plasma K^+ level less than 3.5 mmol/L is called hypokalaemia.

(Ref: Davidson's/20th/432)

Causes of hypokalemia: ***(Very Important for VIVA)***

1. Inadequate intake in diet
2. Loss of K^+ through GIT-
   a) Severe vomiting
   b) Diarrhoea
   c) Nasogastric aspiration
   d) Intestinal fistula
   e) Bowel obstruction
3. Alkalosis due to any cause
4. Endocrine disorders-
   a) Cushing's syndrome
   b) Conn's syndrome
5. Diuretic therapy
6. Corticosteroid therapy
7. Prolonged I.V therapy
8. Insulin excess
9. Mg depletion

(Ref: Davidson's/21st/439,440)

Clinical features / consequences/ effects of hypokalemia:

i) Muscular weakness
ii) Tiredness
iii) Functional bowel obstruction due to paralytic ileus
iv) Hypokalaemic nephropathy
i) Flaccid paralysis
ii) Mental confusion
v) Cardiac arrhythmia
iii) (Finally) cardiac arrest.

(Ref: Davidson's/21st/439)

Diagnosis: Measurement of plasma electrolytes, bicarbonate, urine potassium, and sometimes of Ca & Mg is usually sufficient to establish the diagnosis.

ECG change: Typical ECG changes occur, affecting particularly the T wave.

(Ref: Davidson's /21st/439)

Hyperkalaemia

Q. Write 5 causes of hyperkalaemia. (CU-12Ja)
Q. Short note on: Hyperkalaemia.
Ans.

Hyperkalaemia: Increased plasma K^+ level above the upper limit of normal range (>5 mmol/L), is called hyperkalaemia. But severe hyperkalemia occurs when K^+ level goes above 6.5 mmol/L that can participate in cardiac arrhythmia.

Causes of hyperkalemia: ***(Very Important for VIVA)***

1) Excessive IV infusion
2) Acute and chronic renal failure
3) Acidosis due to any cause
4) Leakage of cellular K^+ in diabetic ketoacedosis
5) Acute starvation
6) Gross haemorrhage
7) Dehydration
8) Adrenocortical failure (Addisons's disease)
9) Drugs (NSAIDs, ACE inhibitors, β-blockers, prolonged heparin therapy, spironolactone)
10) Insulin deficiency and severe hyperglycaemia
11) Severe tissue injury such as-
    a) Massive road traffic accident
    b) Bomb blast
    c) Massive hemolysis
    d) Chemotherapy
    e) Sever burn.

(Ref: Davidson's/21st/439-441; Lecture SSMC)

Clinical features:

1. Progressive muscular weakness
2. Paralysis
3. Diastolic cardiac arrest.

(Ref: Davidson's/21st/440)

Diagnosis: Measurement of plasma electrolytes, creatinine, and bicarbonate.

ECG change: Typical ECG changes occur, peaking of the T wave is an early ECG sign, but widening of the QRS complex presages a dangerous cardiac arrhythmia.

(Ref: Davidson's/21st/440)

Hyponatraemia

Q. Write short note on: Hyponatraemia.
Q. State the causes and effects of hyponatraemia. (RU-07Ja)
Q. What are the features of hyponatraemia? (SU-07Ju)
Ans.
Hyponatraemia: Low levels of sodium in serum below normal (<135 mmol/L) is called hyponatraemia.

Causes of hyponatraemia:

1. **Hypovolaemic hyponatraemia:** (Sodium deficit with a relatively smaller water deficit)
    - Renal Na losses
        - Diuretic therapy (especially thiazide)
        - Adrenocortical failure
    - Gastrointestinal Na losses
        - Vomiting
        - Diarrhoea
    - Skin Na losses
        - Burns
2. **Euvolaemic hyponatraemia:** (Water retention alone)

- Primary polydipsia
- Excessive electrolyte-free water infusion
- Syndrome of inappropriate ADH secretion (SIADH)
- Hypothyroidism

3. **Hypervolaemic hyponatraemia:** (Na retention with relatively greater water retention)
   - Congestive cardiac failure
   - Cirrhosis of liver
   - Nephrotic syndrome
   - Chronic renal failure (during free water intake)

(Ref: Davidson's/21st/435)

Effects/ features of hyponatraemia:

i) May be asymptomatic
ii) Anorexia. nausea & vomiting
iii) Confusion
iv) Lethargy
v) Seizures
vi) Coma
vii) Death.

(Ref: Davidson's/21st/435)

Hypernatraemia

Q. Mention the causes of hypernatraemia. (CMU-21M)
Q. Short note: Hypernatraemia.
Ans.

Hypernatraemia: Increased level of sodium in the serum above normal (>150 mmol/L) is called hypernatraemia.

Causes of hypernatraemia:

1. **Hypovolaemic hyponatraemia:** (Sodium deficit with a relatively greater water deficit)
   - Renal Na losses
     - Diuretic therapy (especially osmotic diuretic, or loop diuretic during water restriction)
     - Glycosuria
   - Gastrointestinal Na losses
     - Colonic diarrhoea
   - Skin Na losses
     - Excessive sweating

2. **Euvolaemic hyponatraemia:** (Water deficit alone)
   - Diabetes insipidus (central or nephrogenic)

3. **Hypervolaemic hyponatraemia:** (Na retention with relatively less water retention)
   - Enteral or parenteral alimentation
   - IV or oral salt administration
   - Chronic renal failure (during water restriction)

(Ref: Davidson's/21st/437)

Clinical features of hypernatraemia:

- Cloudiness
- Dizziness
- Disorientation
- Convulsion
- Confusion

- Weakness
- Coma
- Death.

(Ref: Davidson's/21st/437)

Hypocalcaemia

Q. What are the causes of hypocalcaemia? (RU-08Ju)
Q. Mention 4 causes of hypocalcaemia. (CU-12Ju)
Q. Short note: Hypocalcemia.
Ans.
Hypocalcaemia: Decreased blood calcium level below normal is called hypocalcaemia.

Causes of hypocalcaemia: ***(Very Important for VIVA)***

1. Hypoalbuminaemia
2. Alkalosis
   - Respiratory e.g. hyperventilation
   - Metabolic e.g. Conn's syndrome
3. Vitamin-D deficiency
4. Chronic renal failure
5. Hypoparathyroidism
   - Complication during thyroid surgery
   - Haemochromatosis
   - Wilson's disease
6. Pseudohypoparathyroidism
7. Acute pancreatitis
8. Hypomagnesaemia

(Ref: Davidson's/21st/766)

Clinical feature:

1. Tetany (characteristic triad of carpopedal spasm, stridor and convulsion)
2. Papilloedema
3. Prolongation of the ECG Q-T interval, which may predispose to ventricular arrythmias
4. Epilepsy
5. Psychosis
6. Cataract
7. Rickets in children and osteomalacia in adults.

(Ref: Davidson's/21st/766)

Hypercalcaemia

Q. What are the causes of hypercalcaemia? (RU-08Ju)
Q. Mention 4 causes of hypercalcaemia. (CU-12Ju)
Q. Short note: Hypercalcemia.
Ans.
Hypercalcaemia: Excess blood calcium level above normal is called hypercalcaemia.

Causes of hypercalcaemia:

1. Primary or tertiary hyperparathyroidism
2. Familial hypocalciuric hypercalcaemia

3. Malignancy (e.g. lung, breast, renal, ovarian, colonic & thyroid carcinoma, lymphoma, multiple myeloma)
4. Vitamin D intoxication
5. Thyrotoxicosis
6. Paget's disease with immobilization
7. Granulomatous diseases: e.g. tuberculosis, sarcoidosis
8. Milk-alkali syndrome
9. Thiazide diuretics
10. Glucocorticoid deficiency

(Ref: Davidson's/21st/764-765)

Clinical features:

1. Polyuria
2. Polydipsia
3. Renal colic
4. Lethargy
5. Anorexia
6. Nausea
7. Dyspepsia
8. Peptic ulceration
9. Constipation
10. Depression
11. Drowsiness
12. Impaired cognition.

(Ref: Davidson's/21st/765)

Q. Write the clinical importance of serum calcium. (DU-10Ja)

Ans.

Clinical importance of serum calcium: Please write from above (*where increased and where decreased*).

Acid-Base Disorders

Q. What is the normal pH of blood & urine? (DU-12Ju)

Ans.

Normal pH of blood & urine:

	pH	
	Average	**Range**
Blood	7.45 (arterial), 7.35 (Venous)	7.35-7.45
Urine	6.0	4.5-6.8 (up to 8 in strict vegetarian)
Saliva		6.0-7.0
Milk		6.6-7.0
Tear	7.4	6-8
Pancreatic juice		8-8.3
ICF	7.2	
Bile	7.8	

(Ref: Guyton/11th/794; Orten/10th/881; West &Todd/4th/30)

Metabolic Acidosis

Q. What is metabolic acidosis? (DU-18Nv, CU-17M) **Write down the causes of metabolic acidosis.** (DU-18Nv,16Ja,12Ju,11/05Ja, CU-16/12Ju)

Q. Short note: Metabolic acidosis. (DU-22Nv/M,15/08Ju,07Ja,06S, CU-20Ju,16Ja,15/13/11Ju)
Q. Short note: Causes of metabolic acidosis. (DU-17M)
Ans.
Metabolic acidosis: The primary decrease in plasma [HCO_3^-] arises either from increased production or decreased removal of acids, other than H_2CO_3, or by loss of HCO_3^- from the body, is called metabolic acidosis.

Or,

Decreased p^H due to HCO_3^- deficit is called metabolic acidosis.
Primary defect: ↓ Plasma HCO_3^- due to any cause.
Mechanism / consequence: ↓ Plasma HCO_3^- – → ↓ ratio of $\frac{HCO_3^-}{Pco_2}$ → ↓ pH → metabolic acidosis.

Causes of metabolic acidosis: ***(Very Important for VIVA)***

1. **Addition of excessive metabolic acids to plasma:**
   a. Diabetic ketoacidosis
   b. Prolonged starvation
   c. Lactic acidosis
   d. Methanol poisoning
2. **Failure to excrete acid at a normal rate:**
   a. Renal failure
3. **Loss of HCO_3^-:**
   a. Severe diarrhoea
   b. Intestinal, pancreatic or biliary fistula
   c. Vomiting of intestinal content
   d. Renal tubular acidosis
4. **Drugs:**
   a. K^+ sparing drugs, NH_4Cl, aspirin or methyl alcohol.

Q. Write the lab findings in metabolic acidosis. (CU-16Ju)
Ans.
Lab findings in metabolic acidosis:

1. **pH:** Decreased
2. **Serum HCO_3^-:** ↓ HCO_3^- (primary defect)
3. **P_{CO2}:** ↓ Pco_2 (compensatory response)
4. **HCO_3^-/ PCO_2 ratio:** Decreased
5. **Serum K^+ concentration:** Increased.

Metabolic Alkalosis

Q. What is metabolic alkalosis? (DU-18Nv) **Write the causes of metabolic alkalosis.** (CU-12Ju)
Q. What are the conditions that may lead to metabolic alkalosis? Give the biochemical changes in such patient. (DU-04M)
Q. Short note: Metabolic alkalosis. (DU-09/08Ja,07Ju, BUP-22M)
Ans.
Metabolic alkalosis: Primary increase in plasma [HCO_3^-] due to the accumulation of base or loss of acid other than H_2CO_3 is called metabolic alkalosis.

Or,

Alkalosis characterized by an increase in plasma HCO_3^- and a decrease in plasma [H^+] is called metabolic alkalosis.

Primary defect: ↑ plasma HCO_3^- due to any cause.

Mechanism / consequence: ↑ in plasma HCO_3^- → ↑ratio of $\frac{HCO_3^-}{Pco_2}$ →↑pH→ metabolic alkalosis.

Causes of metabolic alkalosis: ***(Very Important for VIVA)***

a. Administration of diuretics
b. Excess aldosterone secretion
c. Vomiting/aspiration of gastric contents (loss of HCl)
d. Injudicious ingestion of alkaline drugs (e.g. $NaHCO_3$)
e. Migration of H^+ into ICF in K^+ deficiency
f. Massive blood transfusion, containing citrate.

(Ref: Guyton/11th/ 397)

Respiratory Acidosis

Q. Write in short about respiratory acidosis. (DU-21Ja,20Nv/M)

Ans.

Respiratory acidosis: Primary increase in Pco_2, where there is impaired excretion of CO_2.

Or,

A rise in arterial Pco_2 due to hypoventilation with consequent decrease in pH is called respiratory acidosis.

Primary defect: ↑ arterial Pco_2 due to any cause.

Mechanism/consequence: Hypoventilation →↓ CO_2 elimination→↑ arterial Pco_2 →↓ ratio of $\frac{HCO_3^-}{Pco_2}$ →↓ pH→ respiratory acidosis.

Causes of respiratory acidosis: ***(Very Important for VIVA)***

The ultimate cause is **hypoventilation,** which occurs due to-

1. Chronic lung disease e.g. chronic bronchitis, emphysema, pulmonary fibrosis
2. Acute bronchial asthma
3. Acute pulmonary edema
4. Pneumonia
5. Unconscious patient
6. Myesthenia
7. Poliomyelitis
8. Damage of respiratory center (e.g. morphine poisoning)
9. Chest deformities- kyphosis, lordosis etc.

(Ref: Guyton/11th/397; Lecture SSMC)

Respiratory Alkalosis

Q. Short note on: Respiratory alkalosis.

Ans.

Respiratory alkalosis: Primary decrease in plasma Pco_2 due to hyperventilation resulting in increased pH is called respiratory alkalosis.

Primary defect: ↓ Arterial Pco_2, caused by hyperventilation due to any cause.

Mechanism/ consequence: Hyperventilation → ↑CO_2 elimination → ↓ arterial Pco_2 → ↑ ratio of $\frac{HCO_3^-}{Pco_2}$ → ↑ pH→ Respiratory alkalosis.

Causes of respiratory alkalosis: ***(Very Important for VIVA)***

Any cause of *hyperventilation*-

1. High altitude (physiological)
2. Hysterical attacks
3. Salicylate poisoning
4. High fever
5. Meningitis, encephalitis
6. Cerebral tumor
7. Hepatic failure.

(Ref: Lecture SSMC)

Q. A male of 55 years presents with excessive vomiting. He gives history of long standing peptic ulcer disease. What is the likely diagnosis of his present illness? What will be his electrolyte and acid-base status? (DU-16Ju)

Ans.

Diagnosis: Gastric outlet obstruction due to pyloric stenosis (due to long standing peptic ulcer disease).

Acid-base status: Metabolic alkalosis (hypochloraemic metabolic alkalosis).

Electrolyte status:

- Hyponatraemia
- Hypokalaemia
- Hypochloraemia
- Hypocalcaemia.

(Ref: Bailey & Love's/25th/1066)

Q. A 10 year old boy develops severe diarrhoea. What changes you expect in his electrolyte and acid-base status? (DU-10Ja)

Q. Write down the electrolyte pattern of a case of acute diarrhoea. (DU-18Nv)

Ans.

Acid-base status: Metabolic acidosis (*due to loss of HCO_3^- in stools*).

Electrolyte status:

- Hypokalaemia (due to loss of K^+ in stools)
- Hyponatraemia (due to loss of Na^+ in stools and oral intake of free water)
- Hypochloraemia
- Reduced HCO_3^- level.

Q. A male of 65 years with longstanding chronic duodenal ulcer has developed excessive vomiting. What will be his electrolyte and acid-base status? (DU-10/09/08Ju,07Ja)

Ans.

Acid-base status: Metabolic alkalosis (hypochloraemic metabolic alkalosis).

Electrolyte status:

- Hyponatraemia
- Hypokalaemia
- Hypochloraemia
- Hypocalcaemia.

(Ref: Bailey & Love's/25th/1066)

Q. A man aged 25 years is in shock following a road traffic accident. He passed 40 ml urine during last 24 hours. What will be his acid-base and electrolyte status? (DU-09Ja)

Ans.

Acid-base and electrolyte status: The patient is suffering from acute renal failure due to hypovolemia.

Acid-base status: Metabolic acidosis (lactic acidosis).

Electrolyte status:

- Hyperkalaemia *(due to tissue hemolysis and acidosis)*
- Hyponatraemia *(due to excess plasma loss)*
- Hypocalcaemia *(due to renal failure and reduced renal production of 1,25 dihydroxycholecalciferol)*.

CHAPTER 07

ENZYMES OF CLINICAL IMPORTANCE

Q. Write the name of enzymes of clinical importance. (SU-18M,12Ja, RU-17Ju)
Q. Mention role of enzymes of clinical importance. (CU-12Ja, SU-10Ja)
Q. Mention the indication of enzymes of medical importance with examples. (DU-23Nv,21Oct/M)
Q. Name some isoenzymes of clinical importance. (RU-15Ja)

Ans.

Enzymes of clinical importance:

a. Cardiac enzymes:
- Creatine kinase (CK) / creatine phosphokinase (CPK)
- Lactate dehydrogenase (LDH)
- Aspertate aminotransferase (AST)

b. Hepatic enzymes:
- Serum transaminases-
  - AST/ SGOT
  - ALT/ SGPT
- Serum alkaline phosphatase (ALP)
- Serum LDH
- γ-Glutamyl transferase (GGT)

c. Muscle enzymes:
- CPK
- AST
- LDH
- Aldolase

d. Bone enzymes:
- Serum acid phosphatase (ACP)
- Serum ALP

e. Pancreatic enzymes:

- Serum amylase
- Lipase

f. Prostatic disease:
- Prostatic acid phosphatase.

g. Genetic abnormalities:
- Glucose-6-phosphate dehydrogenase
- Pyruvate kinase.

Q. Mention the names of enzymes of clinical importance with their normal values / reference range. (RU-12Ju,11Ja, SU-14Ju,13Ja)
Q. Name the serum enzymes of diagnostic importance. State the normal values and the conditions in which the values are raised. (DU-05Ja, SU-09Ja)
Q. State the clinical significance of alanine transaminase (ALT) (SU-19Nv,17M), **LDH** (CU-14Ju), **alkaline phosphatase** (SU-19Nv,17M, CU-08Ju, RU-04Ja), **creatine kinase** (DU-05S), **acid phosphatase,** (DU-11Ju,05M) **serum amylase** (DU-11Ju,10Ja,08Ju, RU-09Ju) **& γ-glutamyl transferase (GGT).** (RU-09Ju)
Q. Give the clinical importance of AST, ALT, LDH, PSA & serum amylase. (DU-10/08Ja, 10Ju)
Q. Give the importance of acid phosphatase & alkaline phosphatase. (RU-10Ja,08Ju)
Q. Write four causes of high LDH. (CU-09Ja)
Q. Enumerate the different enzymes with their interpretation in various disease conditions. (RU-10Ja)
Q. Name 4 important causes of raised alkaline phosphatase. (CU-10Ju)
Q. Name the hepatic enzymes with their interpretations and normal value/ range. (RU-16/10Ju)
Q. Name clinically important enzymes with their significance. (RU-17Ju)
Q. Short note: Enzymes of clinical importance. (SU-16/15Ja, RU-16Ju,14Ja)
Q. Short note: Alkaline phosphatase. (CU-16/14/12Ja, SU-10Ja)

Ans.

Enzymes of clinical importance:

Enzymes	Normal value (IU/L)	Increased in
1. Aspartate aminotransferase (AST / SGOT)	10 - 45 **(Ref: Davidson's/21st/1296)**	a. **Myocardial infarction** (markedly raised) b. **Non-viral hepatitis** c. Alcoholic liver disease d. Cirrhosis of liver e. Neoplastic disease of liver **(Ref: Davidson's/20th/943)**
2. Alanine aminotransferase (ALT / SGPT)	10 - 50 **(Ref: Davidson's/21st/1296)** ***(ALT is more specific than AST for liver disease)***	a. **Viral hepatitis** ▪ Acute viral hepatitis ▪ Chronic hepatitis B & C b. **Jaundice (hepatocellular & obstructive)** **(Ref: Davidson's/20th/940,943)**
3. Alkaline phosphatase (ALP)	40 - 125 **(Ref: Davidson's/21st/1296)**	a. **Obstructive jaundice** b. Primary biliary cirrhosis b. Metastatic carcinoma of liver c. Non-alcoholic fatty liver disease d. Primary sclerosing cholangitis e. **Paget's disease** f. **Metastatic carcinoma of bone** g. **Osteomalacia and rickets** **(Ref: Davidson's/ 20th/943,972,981,985)**

4. Acid phosphatase	0.5 - 4	a. **Carcinoma of prostate** b. Paget's disease of bone c. Metastatic carcinoma of bone d. Hyperparathyroidism **(Ref: Davidson's/ 20th/511,512)**
5. Lactate dehydrogenase (LDH)	208 - 460 **(Ref: Davidson's/21st/1296)**	a. **Acute myocardial infarction** b. Acute infective hepatitis c. Muscle disease d. Acute leukaemia e. Malignancy f. Megaloblastic anaemia g. Pernicious anaemia h. Haemolytic anaemia i. Pulmonary infection j. Renal necrosis **(Ref: Davidson's/20th/594; Satyanarayana/3rd/107,108; Lecture SSMC)**
6. Creatine kinase (CK)	**Male:** 55-170 **Female:** 30 – 135 **(Ref: Davidson's/ 20th/ 1320)**	a. **Myocardial infarction** b. Muscular dystrophy c. Inflammatory myositis and myopathy d. Motor neuron disease e. Alcohol, drugs f. Trauma, strenuous exercise g. Hypothyroidism **(Ref: Davidson's/20th/1075,1076)**
7. γ-glutamyl transferase (GGT)	**Male:** 10 - 55 **Female:** 5 - 35 **(Ref: Davidson's/21st/1296)**	a. **Liver disease** ▪ Obstructive jaundice ▪ Hepatitis & alcoholic liver cirrhosis ▪ Cholangitis & cholecystitis ▪ Alcohol excess **(Ref: Davidson's/20th/940)**
8. Serum amylase / α-amylase	< 100 **(Ref: Davidson's/21st/1296)**	a. **Acute pancreatitis** b. Intestinal ischaemia c. Perforated peptic ulcer d. Ruptured ovarian cyst **(Ref: Davidson's/20th/905)**

Q. Draw a table showing the role of serum enzyme assay in differentiating various liver disorders. (RU-11Ju)

Q. Mention the enzymes released from diseased liver tissue and state their clinical importance. (RU-10Ju)

Ans.

Role of serum enzyme assay in differentiating various liver disorders:

Enzymes	Increased in liver disorders
1. Aspartate aminotransferase (AST / SGOT)	▪ Non-viral hepatitis (e.g. autoimmune hepatitis, drug induced hepatitis) ▪ Alcoholic liver disease ▪ Cirrhosis of liver ▪ Neoplastic disease of liver
2. Alanine aminotransferase (ALT / SGPT)	▪ Viral hepatitis (more specific)
3. Alkaline phosphatase (ALP)	▪ Obstructive jaundice ▪ Hepatocellular jaundice

4. γ-glutamyl transferase (GGT)	▪ Obstructive jaundice ▪ Hepatitis & alcoholic liver cirrhosis ▪ Cholangitis & cholecystitis ▪ Alcohol excess

Q. Short note: SGPT & SGOT. (CU-09Ja)
Ans.
SGPT & SGOT: Aspartate transaminase (AST / SGOT) & alanine transaminase (ALT / SGPT) function normally to transfer the amino group from an amino acid, alanine in the case of ALT and aspartate in the case of AST, to a ketoacid, producing pyruvate and oxaloacetate respectively.

Both SGOT & SGPT are located in the cytoplasm of the hepatocyte. Although both transaminase enzymes are widely distributed in other tissues of the body, the activities of ALT outside the liver are low, and therefore this enzyme is considered more specific for hepatocellular damage.

(Ref: Davidson's/20th/940)

Normal values and conditions where SGPT & SGOT are increased: *Please write from above.*

Q. Mention the enzymes useful for the diagnosis of myocardial infarction. (RU-15Ja)
Q. Name some cardiac enzymes and proteins that are used to detect myocardial infarction (MI). (DU-13Ja, SU-19Nv,17M)
Q. Mention the enzymes with their interpretation used in myocardial infarction (MI). (SU-20M)
Q. Short note: Cardiac enzymes of clinical importance. (DU-19M,16Ja)
Q. Short note: Cardiac markers. (DU-23M)
Ans.
Cardiac markers: These are intracellular enzymes or proteins released to blood following cardiac muscle damage due to ischemia (e.g. myocardial infarction) or other assaults and shows serial change in plasma concentration with an initial rise followed by a fall.

Types of cardiac markers: Two types-

Enzymes:
1. Creatine phosphokinase (CPK) / Creatine kinase (CK)
2. Aspertate transaminase (AST/ SGOT)
3. Lactate dehydrogenase (LDH)
4. γ-Glutamyl transpeptidase (γ-GTP)

Other proteins:
1) Troponins
2) Myoglobin.

Cardiac markers after MI (myocardial infarction):

Enzymes	Normal value	Enzymatic changes in MI		
		Rise within	Peaks at	Returns to normal in
CK-MB	**Male:** 55 - 170 IU/L **Female:** 30 - 135 IU/L	4 - 6 hours	12-24 hours	48-72 hours
Troponin-I & Troponin-T	Normally absent	4 - 6 hours	24-48 hours	5-14 days
AST	10 - 45 IU/L	12 hours	48 hours	3 - 4 days
LDH	208 - 460 IU/L	12 hours	2 - 3 days	1 - 2 weeks
Myoglobin			6 hours	48 hours

(Ref: Davidson's/23rd/497; Robbins/10th/550; BRS Pathology/5th/138)

Q. Why troponin T & I are the best indicator for MI? (DU-08Ja)
Q. Mention the clinical importance of troponin-I. (RU-15Ja)

Q. Short note: Troponin. (DU-06Ja)

Ans.

Troponin: Troponins are proteins that regulate calcium-mediated contraction of cardiac and skeletal muscle.

Types:

- **Troponin I (TnI):** It is totally **cardio-specific**, hence it is called **cardio-specific troponin-I** (cTn-I).
- **Troponin T (TnT):** It is not totally cardio-specific.
- **Troponin C (TnC):** It is not used as a cardiac marker.

Clinical importance: Troponin I **(TnI)** and troponin T **(TnT)** are ***structural cardiac muscle proteins*** that are released during ***myocyte damage and necrosis***, and represent the ***best indicator for diagnosis of acute MI***, because these markers have ***nearly complete*** **cardiac tissue** ***specificity*** and **high** ***sensitivity***.

Troponin I (TnI) and Troponin T are not normally detectable in the circulation, but following **acute MI**, levels of both cardiac troponins rise at **4 to 6 hours** and peak at **24-48 hours**. Troponin levels remain elevated for **5 to 14 days** after the acute event.

(Ref: Robbin's/10th/550; Davidson's/23rd/450)

(***N.B***: The troponins level may also be elevated in ***minor degrees of myocardial damage***, ***pulmonary embolus***, ***septic shock*** and ***pulmonary oedema***).

(Ref: Davidson's/23rd/450)

Q. Short note: CPK. (CU-10Ju)

Q. Short note: CK. (DU-04S)

Ans.

Creatine kinase (CK) or creatine phosphokinase (CPK): Creatine kinase is an enzyme that is highly concentrated in brain, myocardium, and skeletal muscle and is composed of two dimers, designated "M" and "B".

(Ref: Robbin's/7th/583)

Types / Isoforms:

- **(CK-MM):** Found in skeletal muscle
- **(CK-MB):** Found in cardiac muscle
- **(CK-BB):** Found in brain.

(Ref: Davidson's/20th/1075; Robbin's/10th/550)

Normal value:

Male: 55-170 U/L

Female: 30-135 U/L

(Ref: Davidson's/23rd/1360)

Clinical importance: It is raised in-

a. Myocardial infarction
b. Muscular dystrophy
c. Inflammatory myositis ± vasculitis
d. Motor neuron disease
e. Alcohol, drugs
f. Trauma, strenuous exercise
g. Hypothyroidism, metabolic myopathy.

(Ref: Davidson's/21st/1064)

Q. Write the clinical importance of CK-MB. (DU-11Ju)

Ans.

Creatine kinase MB isoenzyme (CK-MB):

Normal value: < 6% of total CK.

Clinical importance of CK-MB: In myocardial infarction, the CK-MB cardiac-specific isoform is disproportionately elevated compared with total CK.

Enzyme	Normal value	Enzymatic changes in MI		
		Rise within	Peaks at	Remains elevated for
CK-MB	Male: 55 - 170 IU/L Female: 30 - 135 IU/L	4 - 6 hours	12-24 hours	48-72 hours

(Ref: Robbins/10th/550; Davidson's/23rd/497)

Q. A male of 56 years of age presented to you with excruciating left sided chest pain and sweating, not relieved by taking rest and nitroglycerine sublingually. What is your provisional diagnosis? What are the investigations you should advice and their expected clinical results? (DU-11Ja)

Ans.

Provisional diagnosis: Acute myocardial infarction.

Investigations with expected results:

i) **ECG** – ST segment elevation, Pathological Q-wave formation, T-wave inversion.
ii) **CK-MB** – Markedly raised. It starts to rise within 4-6 hours and remains elevated up to 48 to 72 hours.
iii) **Troponin-I** – Markedly raised. It starts to rise within 4-6 hours and remains elevated up to 5 to 14 days.

Q. Name two enzymes acting as tumour marker. (RU-13Ja)

Ans.

Two enzymes acting as tumour marker:

1. **Acid phosphatase:** Marker for carcinoma of prostate and metastatic tumour of bone.
2. **Alkaline phosphatase (ALP):** Marker for metastatic tumour of bone.

Q. Write the clinical importance of PSA. (DU-10/08Ja)

Ans.

Clinical importance of PSA:

1. Measurement of PSA is the most important test used in the diagnosis and management of prostate cancer.
2. 20-40% of patients with a serum PSA > 4.0 ng/ml will have prostate cancer on biopsy.
3. High levels of serum PSA (> 100 ng/ml) almost always indicate distant bone metastases.
4. PSA is most useful for monitoring response to treatment and disease progression.
5. It is also a tumour marker of some breast cancers.

(Ref: Robbins/10th/981; Davidson's/23rd/439,1322,1324)

Q. A 51 year old, chronic alcoholic man was admitted with central abdominal pain radiating to back. His serum amylase was 12000 U/L (Normal <300 U/L). What will be your provisional diagnosis? What type of necrosis will be observed in the peritoneum? (DU-13Ja)

Ans.

Provisional diagnosis: Acute pancreatitis.

Type of necrosis in the peritoneum: Enzymatic fat necrosis.

Q. Short note: ADA. (SU-17M)

Ans.

ADA: Adenosine deaminase (also known as adenosine aminohydrolase, or ADA) is an enzyme involved in purine metabolism. It is needed for the breakdown of adenosine from food and for the turnover of nucleic acids in tissues.

Importance: Its primary function in humans is the development and maintenance of the immune system. However, ADA association has also been observed with epithelial cell differentiation, neurotransmission, and gestation maintenance.

Adenosine deaminase deficiency leads to pulmonary fibrosis.

(Ref: https://en.wikipedia.org/wiki/Adenosine_deaminase)

CHAPTER 08

LIPID AND CHOLESTEROL

Q. What is lipid profile? (DU-13/07Ja, BUP-22Nv,21Nv/M, CMU-21/18M) **Give the normal values.** (DU-17M,13Ja, RU-10Ju)
Q. What are the components of lipid profile (DU-22Nv) **with their normal values / range?** (BUP-21Nv/M, CMU-21M,14Ju, RU-15Ja,10Ju)
Q. Name lipid profile. (DU-17M, SU-14Ju) **What are the fractions of lipid profile?** (DU-07Ja)
Q. Enumerate indications of lipid profile. (RU-10Ju)
Q. Write about lipid profile. (CU-19Nv)
Q. Short note: Lipid Profile. (DU-23Nv,21Oct/M,18Nv,17/14/11/07Ja,06S/Ja, SMU-23M,21Nv, RU-17Ju/Ja,16Ja,13Ju, CU-15Ju/Ja,10/09Ju,08Ja)
Ans.
Lipid profile: The term ***"Lipid profile"*** means the pattern or status of the lipids in plasma.

Or,

The term ***lipid profile*** means "group of laboratory tests done to assess lipid status of an individual and to evaluate risk factors for atherosclerosis and coronary artery disease (CAD)".

Components of lipid profile with their normal values: Lipid profile is commonly determined by the following parameters-

Parameters	Normal value	
	Conventional unit (mg/dl)	SI unit (mmol/L)
1. Total cholesterol (TC)	150 - 220	3.9 - 5.72
2. Triacylglycerol (TAG)	60 - 150	0.6-1.7
3. LDL-cholesterol	< 130	< 3.38
4. HDL-cholesterol	> 40	> 1.0

(To convert **mg/dl** into **mmol/L** multiply by 0.026)

Indications / objectives of lipid profile:

1. Diagnosis of dyslipidaemia
2. Assessment of prognosis for a known dyslipidaemic patient
3. Assessment of risk for atherosclerosis and coronary artery disease.

Preparation of a patient for lipid profile testing:

1. 10-12 hours fasting prior to test
2. Usual diet in previous 3 days (no dietary change allowed)
3. Usual activities in previous 3 days
4. Individual must be free from trauma, surgery, acute infection, pregnancy.

Procedure:

1. Collect fasting morning blood sample
2. Blood is taken in a plain test tube & allowed to clot
3. Serum is separated and lipid profile components are measured.

Clinical importance:

1. Screening for cardiovascular disease
2. Increased LDL directly related to cardiovascular disease
3. Increased HDL inversely related to cardiovascular disease.

(Ref: Davidson's/21st/451,1296; Harper's/25th/869)

Q. Which fraction of lipid profile is better and why? (DU-07Ja)

Ans.

Better fraction of lipid profile: TG is better fraction of lipid profile because it is one of the major treatable risk factors for cardiovascular disease, whilst severe hypertriglyceridaemia also predisposes to acute pancreatitis.

(Ref: Davidson's/21st/449)

Q. Name the blood lipids (plasma lipids) with their normal value.
Q. List the plasma lipids with reference values.

Ans.

Blood lipids with their normal value:

1. **Triacylglycerol (45%):** 53 - 150 mg/dl *(0.6 - 1.7 mmol/L)*
2. **Cholesterol (15%):** 150 - 220 mg/dl *(2.8 - 8.3 mmol/L)*
3. **Phospholipid (35%):** 145 - 200 mg/dl *(1.8 - 5.8 mmol/L)*
4. **Free fatty acid (5%):** 6 - 16 mg/dl *(0.2 - 0.6 mmol/L).*

{**Total lipid:** 450 - 1000 mg/dl.}

(Ref: Harper's/25th/269; Davidson's/21st/1296)

Q. Write down the important causes of hyper cholesterolaemia. (CU-08Ju)
Q. Write the causes of high and low value of serum cholesterol. (CU-12Ja)
Q. Mention the causes of hyperlipidaemia. (CMU-22Nv/M,21Nv,20Nv/M,10Ja, SU-20Nv,16/15Ja, RU-15Ja)
Q. Short note: Dyslipidaemia. (DU-11Ju, SU-19M)
Q. Short note: Hyperlipidaemia. (SU-15/13/09Ju,08Ja)

Ans.

Dyslipidaemia: Abnormalities in lipid profile is called dyslipidaemia.

Hyperlipidaemia: Excess lipid in blood is called hyperlipidaemia.

Hypercholesterolaemia: Increased cholesterol level in blood above normal is called hypercholesterolaemia (> 300 mg /dl).

Causes of hyperlipidaemia:

A. **Hypercholesterolaemia:**
   1. **Primary** - Familial hypercholesterolaemia
   2. **Secondary hypercholesterolaemia:**

- Hypothyroidism
- Pregnancy
- Cholestatic liver disease
- Drugs (diuretics, corticosteroids, androgens)
- Nephrotic syndrome
- Anorexia nervosa
- Porphyria
- Hyperparathyroidism

B. <u>Hypertriglyceridaemia</u>:

1. **Primary** - Familial hypertriglyceridaemia
2. **Secondary hypertriglyceridaemia:**
   - Diabetes mellitus (type 2)
   - Chronic renal disease
   - Abdominal obesity
   - Excess alcohol
   - Hepatocellular disease
   - Drugs (β-blockers, retinoids, corticosteroids).

(Ref: Davidson's/21st/451-456)

Q. How will you diagnose a case of dyslipidaemia? (DU-22Nv)

Ans.

<u>Approach to diagnose a case of dyslipidaemia</u>:

A. History:
- Obesity
- Diabetes
- Hypertension
- Nephrotic syndrome
- Occasional severe abdominal pain (H/O pancreatitis)
- Family history of dyslipidaemia
- Hypothyroidism
- Drugs – OCP, steroid, thiazide, β-blocker etc.
- Alcohol intake
- Dietary habit

B. Physical examination: Corneal arcus, xanthalesma, eruptive xanthoma, tendon xanthoma.

C. Lab. investigations: Estimation of serum lipid profile.

(Ref: Lecture AFIP)

Q. Short note: Lipoprotein. (DU-12Ju)

Ans.

<u>Lipoprotein</u>: Lipoproteins are complex lipid made up of lipid and protein *(called apolipoproteins or apoproteins)* means for transport of lipid in blood.

(Ref: Lippincott's/5th/227)

<u>Classification of lipoproteins</u>: Four major groups of plasma lipoproteins have been identified-

1. Chylomicrons
2. Very-low density lipoproteins (VLDL) or, pre-β-Lipoproteins
3. Low-density lipoproteins (LDL) or, β-Lipoproteins
4. High-density lipoproteins (HDL) or, α-Lipoproteins.

<u>Constituents of lipoprotein</u>:

1. Triacylglycerol (TAG)
2. Phospholipid
3. Free cholesterol

4. Cholesteryl ester
5. Apoprotein

Structure of lipoprotein: A typical lipoprotein consists of-

1. **A lipid core**-containing non polar triglyceride and cholesteryl ester.
2. **A single surface layer of phospholipid, free cholesterol and apoproteins.** Phospholipid and cholesterol are so oriented that their polar groups face outward to the aqueous medium, making the particle water soluble.

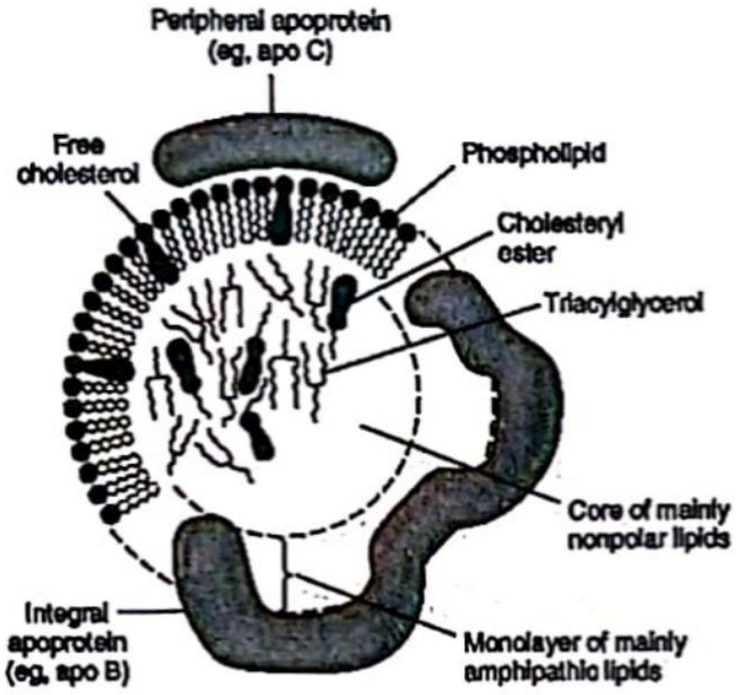


Fig: Structure of a lipoprotein.

Functions of lipoproteins: Since lipids are insoluble in water, they cannot alone travel in the aqueous blood plasma. Lipoproteins are water soluble. So lipids can easily travel in blood as lipoprotein. So lipoproteins act as transport vehicle for lipid in plasma.

1. **Chylomicrons:** Transport exogenous **TAG** from **intestine to liver & peripheral tissue.**
2. **VLDL:**
   - Transport endogenously synthesized **TAG** from **liver to peripheral tissue.**
   - Acts as precursor of LDL
3. **LDL:** Transport **cholesterol** from **liver to peripheral tissue.**
4. **HDL:** Transport **cholesterol** from **peripheral tissues to liver** for its degradation and excretion ***(Reverse cholesterol transporter).***

Blood levels of lipoproteins:

Type of lipoprotein	Origin	Main lipid content	Blood level (mg/dl)
Chylomicron	Intestine	TAG	100 - 200
VLDL	Liver	TAG	< 40
LDL	From VLDL in blood	Cholesterol	< 130
HDL	Liver and intestine	Phospholipids	> 40

Clinical importance:

1. High LDL level causes increased cholesterol deposition in arterial wall resulting in atherosclerosis.
2. HDL removes cholesterol from peripheral tissues and thus prevents formation of atherosclerosis.
3. Imbalance in the rate of TG formation in liver and in VLDL secretion leads to fatty liver.

(Ref: Harper's/28th/213-215; Lippincott's/5th/227,228)

Q. Name the atherogenic lipoproteins.

Ans.

Atherogenic lipoproteins:

- VLDL
- LDL

- VLDL remnant
- Chylomicron remnant
- Lp (a).

Q. What is the significance of LDL?
Q. Short note: LDL.
Ans.
LDL (Low density lipoproteins): LDL is one of the four major groups of lipoproteins, representing a final stage in the catabolism of VLDL.

Synonym: β-lipoprotein.

Origin/source: From VLDL (in the plasma).

Diameter: 20-25 mm.

Density: 1.019-1.063 gm/ml.

Composition:
1. Protein 21%
2. Lipid 79%

Main lipid components:
1. High concentration of cholesterol, phospholipid & cholesterol ester.
2. Low concentration of triacylglycerol.

Significance of LDL:
1. Low density lipoproteins (LDL) transport cholesterol from liver to peripheral tissue.
2. It may be responsible for atherosclerosis which may lead to-
   - Myocardial infarction
   - Stroke (cerebral infarction)
   - Peripheral arterial thrombosis leads to gangrene
   - So, increased LDL is harmful to our body.

(Ref: Lippincott's/3rd/229-232; Harper's/28th/212-219)

Q. Name the anti-atherogenic lipoproteins. Describe the role of HDL-cholesterol.
Q. What is the clinical importance of HDL? (CU-09Ja)
Q. Why HDL is beneficial for our health, explain? (DU-22Nv)
Ans.
Anti-atherogenic lipoprotein: HDL.

Role of HDL-cholesterol: HDL transports cholesterol form the **peripheral tissue to the liver**. In the liver, this cholesterol can be either repackaged into lipoproteins, converted into bile acids or secreted into the bile in unchanged form for removal from the body. So, the more the HDL-cholesterol, the less the cholesterol deposition in peripheral tissue and the ***less chance of atherosclerosis***. That is why HDL is known as **anti-atherogenic** or, sometimes called "**good cholesterol**".

A high level of HDL-C seems to protect against cardiovascular diseases, and low HDL cholesterol levels (less than 40 mg/dL) increase the risk for heart disease. So, HDL particle is considered as **protection to the body's cardiovascular health**. So it is **good / beneficial** for health.

(Ref: Harper's/29th/242; Lippincott's/5th/234-237)

Q. Short notes: HDL. (RU-09Ju)
Ans.
HDL: It is a lipoprotein having highest density.

Synonym: α-lipoprotein.

Composition:

HDL	Sources	Main lipid component	Apoprotein
HDL_1	Liver Intestine	Phospholipid Cholesterol Cholesteryl ester TAG	A, C, B, E, A-I
HDL_2			
HDL_3			
Pre β-HDL			

Role of HDL-cholesterol: HDL transports *cholesterol* form the **peripheral tissues to the liver** ***(Reverse cholesterol transporter)***. In the liver, this cholesterol can be either repackaged into lipoproteins, converted into bile acids or secreted into the bile in unchanged form for removal from the body. So, the more the HDL-cholesterol, the less the cholesterol deposition in peripheral tissue and the less chance of atherosclerosis. That is why HDL is known as ***anti-atherogenic*** or, sometimes called ***"good cholesterol"***.

A high level of HDL-C seems to protect against cardiovascular diseases, and low HDL cholesterol levels (less than 40 mg/dL) increase the risk for heart disease. So, HDL particle is considered as protection to the body's cardiovascular health.

(Ref: Harper's/29th/242; Lippincott's/5th/234-237)

Q. What is good and bad cholesterol? Why they are called so? (BUP-21Nv/M)
Q. Why HDL is called good cholesterol (BUP-22M) **and LDL is bad cholesterol?** (DU-23Nv,08Ja)
Ans.
HDL is called good cholesterol and LDL is bad cholesterol: HDL is called ***good cholesterol***, because HDL removes cholesterol from the peripheral tissues to the liver where it is metabolized and excreted in bile, thus it ***reduces tissue atherogenecity.***

On the other hand, LDL is called ***bad cholesterol***, because LDL carries cholesterol from the liver to the peripheral tissues, thus it ***increases tissue atherogenecity***.

(Ref: Davidson's/21st/451)

Q. State the differences between LDL and HDL. (SU-20Nv)
Q. How LDL differs from HDL? (SU-16Ja)
Ans.
State the differences between LDL and HDL cholesterol:

Traits	LDL	HDL
Synonym	β-lipoprotein	α-lipoprotein
Origin	From VLDL (in blood)	Liver and intestine
Main lipid content	Cholesterol	Phospholipid
Blood level (mg/dl)	< 130	> 40
Function	Carries cholesterol from the liver to the peripheral tissues	Carries cholesterol form the peripheral tissues to the liver (reverse cholesterol transporter)
Role on atherogenecity	Increases tissue atherogenecity	Reduces tissue atherogenecity
Functional name	Atherogenic / bad cholesterol	Anti-atherogenic / good cholesterol

CHAPTER 09

PREGNANCY TEST

Q. Enumerate the indications of pregnancy test. (CMU-23M,15/12Ja, RMU-21Nv,14Ja,12/11/10/09Ju,07Ja)
Q. Mention the methods employed in pregnancy test. (RU-14Ja,10Ju)
Q. Short note on: Pregnancy test. (DU-23/06M)
Ans.

Pregnancy test: Pregnancy test based on the presence of HCG in the urine and blood. **In blood**- as early as 6 days after conception. **In urine**- as early as 14 days after conception.

(Ref: Lecture SSMC)

Indications:

1. Diagnosis of pregnancy in an early stage
2. Confirmation when the foetus is suspected to be dead
3. Diagnosis of hydatidiform mole and choriocarcinoma
4. Diagnosis of pseudocyst.

Principle: The presence of HCG in the urine of pregnant woman forms the basis of all pregnancy tests. Immunologically pregnancy can be diagnosed by the test involving the principle of antigen antibody reaction.

(Ref: Samson Wright's/13th/581)

Tests:

1. **Modern methods :** Immunological tests- (**advantage**-cheap, reliable, accurate and quick result)
   - Direct agglutination test
   - Indirect agglutination test
2. **Biological methods:** (**advantage** -99% accurate; **disadvantage**-costly, time consuming)
   - Fried man test
   - Ascheim-Zondec test
   - Female xenopus laevis test.
   - Galli manini test
3. Radioimmunoassay (RIA)
4. Enzyme-linked immunosorbent assay (ELISA)
5. Ultrasonography
6. Radiological test.

(Ref: Lecture SSMC)

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a) Pyelonephritis (F)
b) Toxaemia of pregnancy (T)
c) Nephrotic syndrome (T)
d) Acute glomerulonephritis (F)
e) Renal cell carcinoma (F)

Q. Causes of ketonuria include - (DU-11Ja)
a) Untreated diabetes mellitus (T)
b) Starvation (T)
c) Severe dehydration (T)
d) Diet low in fat (F)
e) Obesity (F)

Q. Causes of hyperuricaemia include - (DU-10Ju/J,09Ju)
a) Gout (T)
b) Liver damage (F)
c) Psoriasis (T)
d) Allopurinol (F)
e) Alcoholism (F)

Q. Urinary protein can be detected by - (DU-10Ju)
a) Heat coagulation test (T)
b) Benedict test (F)
c) Sulphosalycylic acid test (T)
d) Hams test (F)
e) Rothera's test (F)

Q. Causes of ketonuria are - (DU-10Ja)
a) Untreated diabetes (T)
b) Severe dehydration (T)
c) Glycogen storage disease (T)
d) Diet high in carbohydrate (F)
e) Decreased fat metabolism (F)

Q. Massive proteinuria occurs in - (DU-10Ja)
a) Chronic renal failure (F)
b) Hepatic failure (F)
c) Nephrotic syndrome (T)
d) Minimal change disease (T)
e) SLE (T)

Q. The blood urea is elevated in - (DU-09Ju)
a) Severe dehydration (T)
b) Pregnancy (F)
c) Tubular necrosis (T)
d) Diabetes insipidus (F)
e) Cortical necrosis (T)

Q. The nephrotic syndrome is accompanied by - (DU-09Ju)
a) Decreased glomerular capillary permeability (F)
b) Oedema (T)
c) A loss of 4 gm or more of plasma protein daily (T)
d) Hypolipidaemia (F)
e) Abundant cortical deposits of neutral fat (T)

Q. Characteristic features of Bence Jones protein - (DU-09Ja)
a) Free monoclonal kappa or lambda chain (T)
b) Originally described for behaviour on heating (T)
c) It flocculates when heated to 300°C (F)
d) Also found occasionally in lymphoma (F)
e) Electrophoresis of urine is a non-reliable method (F)

Q. Renal function tests include - (DU-09Ja)
a) Renal clearance test (T)
b) Blood urea-nitrogen (T)
c) Serum uric acid (T)
d) Urea clearance test to assess renal blood flow (F)
e) Inulin clearance test to assess GFR (T)

Q. The following conditions are associated with alkaline urine - (DU-09Ja)
a) Vegetarian diet (T)
b) Muscular fatigue (T)
c) Urinary tract infection with E. coli (F)
d) Systemic alkalosis (T)
e) Non-ketotic acidosis (F)

Q. Causes of hyperuricaemia include - (DU-08Ju)
a) Gout (T)
b) Alcoholism (F)
c) Liver damage (F)
d) Large dose of vitamin-C (F)
e) Leukemia (T)

Blood Glucose & Diabetes Mellitus

Q. Characteristics of type I diabetes mellitus includes- (DU-23M)
a) increased age (F)
b) obesity (F)
c) linkage with HILA-B_{27} (T)
d) beta cell destruction (T)
e) frequent ketoacidosis (T)

Q. Characteristics of type-I DM: (DU-22Nv)
a) Markedly reduce blood insulin (F)

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b) Insulin resistance (T)
c) Younger age (F)
d) Beta cell destruction (F)
e) Linkage to HLA gene (F)

Q. Type-I DM is characterized by: (DU-22M,20Nv/M)
a) Early onset (T)
b) Patients are commonly obese (F)
c) Associated with significant genetic factor (F)
d) Autoimmune destruction of islet cells (T)
e) Hypoglycaemic coma is frequent (F)

Q. Causes of hypoglycemia are- (RMU-22M)
a) Diabetes mellitus (F)
b) Insulinoma (T)
c) Addison's disease (F)
d) Acromegaly (F)
e) Pregnancy (F)

Q. Following features are associated with hyperglycaemia sine glycosuria- (DU-21Oct/M)
a) Presence of sugar in urine (F)
b) Low renal threshold for glucose (F)
c) Found in uncontrolled DM (T)
d) Metabolic acidosis (T)
e) Hyperkalemia (T)

Q. Causes of hyperglycemia includes- (DU-21Ja,20Nv/M,18Ja)
a) Diabetes mellitus (T)
b) Hyperadrenalism (T)
c) Insulin overdose (F)
d) Septic shock (F)
e) Heavy exercise (F)

Q. Glycosuria may occur in: (CU-19Nv)
a) Diabetes mellitus (T)
b) Cushing syndrome (T)
c) Chronic glomerulonephritis (F)
d) Hyperthyroidism (T)
e) Urinarv tract infection (F)

Q. Oral glucose tolerance test done in- (RU-19M)
a) Gestational diabetes (T)
b) Hyperthyroidism (F)
c) Liver disease (F)
d) Impaired glucose tolerance (T)
e) Hypoglycaemia (F)

Q. Hypoglycemia occurs in- (DU-18M)
a) Insulinoma (T)
b) Cushing syndrome (F)
c) Septic shock (F)
d) Missed meal of diabetics (T)
e) Burn (F)

Q. Following are causes of glycosuria - (RU-17M)
a) Partial gastrectomy (T)
b) Intestinal obstruction (F)
c) Insulinoma (F)
d) Increased renal threshold for glucose (F)
e) Pregnancy (T)

Q. Causes of hyperglycemia includes - (DU-17Ja)
a) Grave's disease (T)
b) Hashimoto thyroiditis (F)
c) Myxedema (F)
d) Insulinoma (F)
e) Diabetes insipidus (F)

Q. Indications of GTT are- (DU-14Ju)
a) pregnancy related diabetes (F)
b) IGT (T)
c) alimentary glycosuria (F)
d) longstanding hypertension (F)
e) hyperthyroidism (F)

Q. Ketonuria may occur in- (DU-14Ju)
a) severe diabetes mellitus (T)
b) diabetes insipidus (F)
c) prolonged starvation (T)
d) uremia (F)
e) cachectic person (T)

Q. The indication of GTT are - (DU-14Ja)
a) To detect hyperglycemia (T)
b) To diagnose endocrine disorder (F)
c) Alimentary glycosuria (F)
d) To diagnose diabetes incipidus (F)
e) To find out the cause of coma or convulsion (F)

Q. Causes of hypoglycaemia - (RU-13Ju)
a) Overdose of insulin (T)
b) Diabetes mellitus (F)
c) Addison's disease (T)
d) Insulinoma (T)
e) Acromegally (F)

Q. Causes of ketosis - (RU-13Ju)
a) Severe diabetis mellitus (T)
b) Persistent vomiting (T)
c) Nephritic syndrome (F)
d) Ischemic heart disease (F)

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e) CCF (F)

Q. Endocrinopathies leading to diabetes mellitus include - (DU-12Ja)
a) Cushing syndrome (T)
b) hypothyroidism (F)
c) glucagonoma (T)
d) pituitary adenoma (T)
e) acute renal failure (F)

Q. Causes of hypoglycaemia are - (DU-09Ja)
a) Excess insulin (T)
b) Liver disease (T)
c) Alcoholism (T)
d) Gushing syndrome (F)
e) Steroid administration (F)

Semen Analysis

Q. Normal semen is characterized by- (DU-18Ja)
a) Two to five ml per ejaculation (T)
b) Sperm count 20 million per ml. (T)
c) >70 % motile in first hour (F)
d) 50% normal in morphology (T)
e) Within half an hour liquefied (F)

Q. Semen analysis - (RU-13Ju)
a) Normal liquefaction time is 20-30 minute (F)
b) Sperm <20 m/ml is oligospermia (T)
c) Prolonged liquefaction time indicates sterility (T)
d) 40 m/ml sperm count is hyperzoospermia (F)
e) No spermatozoa either living or dead is called asthenozzospermia (F)

Q. Indication of semen analysis include - (DU-12Ju)
a) undescended testis (F)
b) following vasectomy (T)
c) hypogonadism (F)
d) testicular neoplasm (F)
e) following chemotherapy (F)

Q. Indication of semen analysis are- (DU-11Ju)
a) infertility (T)
b) paternity test (T)
c) after vagotomy (F)
d) rape (T)
e) after vasectomy (T)

Body Fluids

Q. Macroscopic changes of CSF in pyogenic meningitis: (DU-23Nv)
a) Cobweb formation (F)
b) Coarse coagulation formation (T)
c) Crystal clear in appearance (F)
d) Xanthochromic in colour (F)
e) Turbid in appearance (T)

Q. CSF findings of pyogenic meningitis: (DU-22Nv)
a) Opening pressure is increased (T)
b) Coagulum is present (T)
c) Crystal clear (F)
d) Reduced sugar concentration (T)
e) Rich in lymphocytes (F)

Q. Features of CSF in pyogenic meningitis include: (DU-22M,18/117Nv)
a) Lymphocytic pleocytosis (F)
b) Increased sugar (F)
c) Decreased protein (F)
d) Hazy in appearance (T)
e) Cobweb formation (F)

Q. Changes of CSF findings in tubercular meningitis - (DU-19M)
a) Neutrophil pleocytosis (F)
b) Decreased protein content (F)
c) Cob-web formation (T)
d) Decreased chloride content (T)
e) Decreased sugar content (T)

Q. Followings are associated with viral meningitis - (RU-18M)
a) Clear CSF (T)
b) Lymphocyte in CSF (T)
c) Neutrophil in CSF (F)
d) Clot formation (F)
e) Blood in CSF (F)

Q. Exudative pleural effusion occurs in- (DU-16Ju)
a) Pulmonary tuberculosis (T)
b) Nephrotic syndrome (F)
c) Bronchogenic carcinoma (T)
d) Pneumonia (T)
e) Cardiac failure (F)

Q. CSF findings in tubercular meningitis include- (DU-16Ju)
a) Increased pressure (T)

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d) Conn's syndrome (F)
e) Milk-alkali syndrome (F)

Q. Causes of metabolic acidosis include: (DU-18M)
a) Uncontrolled diabetes mellitus (T)
b) Diarrhea (T)
c) Primary hyperaldosteronism (F)
d) Severe vomiting (T)
e) Shock (F)

Q. Causes of metabolic acidosis are (DU-18M)
a) Excessive vomiting (T)
b) Increase alkali intake (F)
c) Excessive diarrhea (T)
d) Uncontrolled diabetes mellitus (T)
e) Prolonged starvation (F)

Q. Causes of metabolic acidosis are: (DU-17Ja)
a) excessive vomiting (T)
b) increased alkali intake (F)
c) excessive diarrhea (T)
d) DIC (F)
e) head injury (F)

Q. Causes of hyperkalaemia include: (DU-16Ju)
a) Haemolysis(T)
b) Treatment with thiazide diuretic (F)
c) Acidosis (T)
d) Diarrhoea (F)
e) Hyperaldosteronism (F)

Q. Causes of hypokalemia include: (DU-16Ja)
a) metabolic alkalosis (T)
b) respiratory acidosis (F)
c) acute renal failure (F)
d) cushing syndrome (T)
e) secondary aldosteronism (T)

Q. Causes of hypercalcaemia include: (DU-15Ju)
a) Hyperparathyroidism (T)
b) Sarcoidosis (T)
c) Vitamin A deficiency (F)
d) Malabsorption (F)
e) Menopause (F)

Q. Causes of metabolic alkalosis are: (DU-15Ja)
a) Potassium depletion (F)
b) Gushing syndrome (T)
c) Severe diarrhea (T)
d) Shock (F)
e) Conn's syndrome (T)

Q. Causes of hypercalcemia include: (DU-14Ju)
a) hyperparathyroidism (T)
b) multiple myeloma (T)
c) malabsorption syndrome (F)
d) sarcoidosis (T)
e) gout (F)

Q. Metabolic acidosis may be due to - (DU-14Ja)
a) Overdose of insulin (F)
b) Uncontrolled diabetes mellitus (T)
c) Ketoacidosis (T)
d) Hyperventillation (T)
e) Excessive vomiting (T)

Q. Metabolic alkalosis can be due to - (DU-13Ju)
a) excessive vomiting (T)
b) intake of alkali (T)
c) acute renal failure (F)
d) complication of uncontrolled diabetes mellitus (F)
e) hyperventilation (F)

Q. Causes of metabolic acidosis are - (DU-13/12J,11/10/08Ju)
a) Ketoacidosis (T)
b) Chronic renal failure (T)
c) Vomiting (F)
d) Gushing syndrome (F)
e) Acute renal failure (T)

Q. Following conditions are associated with hypokalemia - (DU-12Ju)
a) end-stage of renal failure (F)
b) adrenal insufficiency (F)
c) metabolic alkalosis (T)
d) nasogastric suction (T)
e) rhabdomyolysis (F)

Q. Causes of hypocalcaemia include - (DU-09Ja)
a) Hypoparathyroidism (T)
b) Renal failure (T)
c) Sarcoidosis (F)
d) Hypervitaminosis D (F)
e) Malabsorption (T)

Q. Causes of hyponatraemia include - (DU-08Ju)
a) Excess ADH secretion (F)
b) Congestive cardiac failure (T)
c) Diuretics (T)
d) Dehydration (F)
e) Excessive ingestion of salt (F)

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Enzymes

Q. Enzymes of medical importance are: (DU-17Ja)
a) amylase (T)
b) CPK (T)
c) lactate dehydrogenase (T)
d) acid phosphatase (T)
e) aldolase (T)

Q. Biochemical markers of acute MI includes - (RU-14Ja,13Ju)
a) Troponin-T (T)
b) LDH (T)
c) Alkaline phosphatase (F)
d) CK-MB (T)
e) γ-interferon (F)

Q. Raised serum acid phosphatase include - (DU-12Ju)
a) Paget's disease of bone (T)
b) rickets (F)
c) chronic liver disease (F)
d) chronic prostatitis (T)
e) osteoporosis (F)

Q. The preferred biochemical markers for diagnosis of acute myocardial infarction include - (DU-10Ja)
a) LDH (T)
b) Troponin-I (T)
c) CK-MB (T)
d) Troponin-T (T)
e) SGPT (F)

Q. Following statements are true for alkaline phosphatase - (DU-08Ju)
a) Produced in bone cells and liver (T)
b) Increases in Paget's disease (T)
c) Marked increase in obstructive jaundice (T)
d) Increases in malnutrition (F)
e) Increases in pernicious anaemia (F)

Blood Lipids

Q. Hyperlipidaemia mostly occurs in: (DU-23Nv)
a) Nephrotic syndrome (T)
b) Long term starvation (F)
c) Diabetes mellitus (T)
d) Pulmonary hypertension (F)
e) Obesity (T)

Q. Secondary causes of dyslipidaemia includes- (DU-21Oct/M)
a) hyperthyroidism (F)
b) nephritic syndrome (T)
c) Intra-hepatic cholestasis (T)
d) diabetes mellitus (T)
e) Prolong use of corticosteroid (T)

Q. Hypercholesterolaemia occurs in: (DU-21Ja,20Nv/M,17M)
a) hyperthyroidism (F)
b) chronic anemia (F)
c) diabetes mellitus (T)
d) nephritic syndrome (T)
e) Cushing syndrome (F)

Q. Hyperlipidaemia commonly occurs in: (DU-19M)
a) Nephrotic syndrome (T)
b) Diabetes mellitus (T)
c) Hyperthyroidism (F)
d) Adrenal insufficiency (F)
e) Nephritic syndrome (F)

Q. Hyperlipidaemia occurs in - (DU-17Ja)
a) familial hypercholesterolaemia (T)
b) diabetes mellitus (T)
c) nephrotic syndrome (T)
d) nephritic syndrome (F)
e) peptic ulcer disease (F)

Q. Hyperlipidaemia occurs in: (DU-15Ju)
a) Diabetes mellitus (T)
b) Nephrotic syndrome (T)
c) Hyperthyroidism (F)
d) Cushing syndrome (T)
e) Hyperparathyroidism (T)

Q. Hypercholesterolaemia occurs in: (DU-14Ju)
a) hyperthyroidism (F)
b) anemia (F)
c) diabetes mellitus (T)
d) nephritic syndrome (T)
e) liver disease (T)

Q. Hypercholesterolemia occurs in - (DU-13Ja,12Ju)
a) Hyperthyroidism (F)
b) Anaemia (F)
c) Diabetes mellitus (T)
d) Nephritis syndrome (F)
e) Liver disease (T)

Q. A normal lipid profile include - (DU-10/09Ju)
a) Low serum cholesterol (T)

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b) Increased high density cholesterol (T)
c) Increased triglycerides (F)
d) Decreased very low density lipoproteins (T)
e) Low apo-lipoproteins (F)

Stool Examination

Q. Occult blood test is positive in: (DU-15Ja)
a) Obstructive jaundice (F)
b) Bleeding PUD (T)
c) Ca stomach (T)
d) Ca gall bladder (F)
e) Ulcerative colitis (T)

Miscellaneous

Q. Following are correctly matched - (RU-18M)
a) Ketonuria – old diabetes mellitus (T)
b) Increased number of lymphocytes – pyogenic meningitis (F)
c) Increased PT – overdose of anticoagulant (T)
d) Pseudocyasis – positive pregnancy test (T).
e) ↓ albumin globulin ratio – Crohn's disease (F)

Q. The following values are within normal limit - (DU-13Ja)
a) FBS: 5.5 milimol/litre (T)
b) S. creatinine: 3.4 mg/dl (F)
c) Blood urea: 120 mg/dl (F)
d) Triglyceride: 180 mg/dl (F)
e) Serum PSA: 0.4 U/L (T)

Q. The Coomb's test is used for detecting - (DU-10/08Ju)
a) Rheumatoid factor (F)
b) Anti-nuclear factor (F)
c) Haemolytic autoantibodies (T)
d) Cold agglutinins (T)
e) Rhesus antibodies (F)

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